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JULY 1942

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Oct. 20, 1917, at the Postoffice at Chicago, Ill.
Under the Act of Congress of March 3, 1879

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# EPITHELIOMA OF THE SKIN

## MANNER OF GROWTH: HISTOLOGIC STUDY OF WHOLE TUMOR SECTIONS

RICHARD L. SUTTON JR., M.D., F.R.C.S. (Edin.)
Assistant Professor of Dermatology, University of Kansas School of Medicine, Kansas City, Kan.

KANSAS CITY, MO.

As a carcinoma grows, it expands laterally as well as in depth. Starting in known cancerous tissue near the middle of a lesion and moving radially outward, one must reach eventually an external region where all epithelium is known to be normal; hence transition zones must exist. My study concerns these zones where neoplastic and normal epithelium lie close together. The question is considered whether there occurs intergradient transition of cell type between obviously normal and obviously neoplastic cells or, alternatively, whether the normal cells are of one kind, the neoplastic ones of another kind and their spacial relation merely juxtaposition. Does "progressive cancerization" of normal epithelium occur at the boundary of a growing carcinoma?

### MATERIALS AND METHODS

My material consists of whole tumor sections of some sixteen hundred cutaneous lesions. Most of the tumors were excised along with margins of normal skin by means of the actual cautery. Fixed in formaldehyde, they were sent to Col. W. F. Harvey, director of the Royal College of Physicians Laboratory, Edinburgh, Scotland, where paraffin sections of carefully orientated blocks were stained with hematoxylin and eosin. Several sections of a tumor were mounted on each slide, of which Colonel Harvey and I possess duplicates. Serial sections have not been made, but in some cases I have examined twelve sections of one tumor. The sections were cut perpendicular to the skin and approximately through the middle of the tumor. Such preparations differ considerably from ordinary specimens for biopsy. Ten of them were selected for detailed presentation in photomicrographs. Practically all the photomicrographs I made using the Wratten B (green) filter. The method of making photomicrographs of considerable areas of tissue was reported previously.[1] Some photographic difficulty due to waviness of mounted

1. Sutton, R. L., Jr.: Early Epidermal Neoplasia: Description and Interpretation; the Theory of Mutation in the Origin of Cancer, Arch. Dermat. & Syph. **37**:737-777 (May) 1938.

tissues was met by compressing slides between smooth heavy objects held tightly together by rubber bands and kept warm in an incubator for from twenty-four to forty-eight hours. Warping recurs, and flattened tissues must be photographed promptly.

### CELLULAR NATURE OF CARCINOMA AND HISTOLOGIC INVESTIGATION

In my description [1] of early epidermal neoplasms, I argued that cancer is a cellular disease:

It begins in one or at the most in only a few cells. . . . Given the existence of neoplastic cells, it is my belief that their gross and microscopic appearance and behavior are properly analyzable in terms of two physical aspects: their rate of proliferation and their tendency to cling to one another. By coherence I mean a property which is much in evidence in the epithelium of a cutaneous horn, in contrast with its lack in the epithelium of those senile keratoses which bleed easily and scale off readily.

Cowdry [2] wrote:

Epithelial cells that grow in sheets naturally stick together. . . .

Malignant cells arising in the stratum spinosum of the epidermis cannot break away and invade the deeper tissues until the typically firm connections with their neighbors are loosened. In benign epithelial tumors the cells stick together in arrangements resembling normal cell aggregates; with increase in malignancy, they relinquish this property more and more and strike out for themselves. Perhaps decrease in stickiness of carcinomatous cells is a necessary prelude to their invasiveness.

Concerning the cellular nature of carcinoma, I quote from Foulds's review [3]:

The structure and clinical behaviour of most of the individual [transplanted] tumour strains remain remarkably constant over long periods of time. . . . Some tumours have been maintained by serial transplantation for more than thirty years without substantial change. . . . Constancy of structure and of behaviour however is not invariable in transplanted tumours. Strong and others have described sudden irreversible changes, which they term "mutations," during the transplantation of mouse tumours. . . .

The form and arrangement of cells are modified by mechanical factors such as mutual compression or lack of support. . . . In histiogenetic classifications it is assumed, probably correctly, that the differentiations in tumours are limited to those which the parent tissue can manifest. . . . It is probable that all the possible differentiations of a tissue can be revealed in the various tumours to which it gives origin, but some differentiations are common and others rare and . . . the majority of tumours derived from a single tissue can be classified in a few fairly well defined groups. . . .

Experimental investigations of tumours allow the following deductions:

1. Tumours, with rare exceptions, retain permanently those genetic properties which distinguish the tissues of one animal species from those of all other species.

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2. Cowdry, E. V.: Properties of Cancer Cells, Arch. Path. **30**:1245-1274 (Dec.) 1940.

3. Foulds, L.: The Histological Analysis of Tumours: A Critical Review, Am. J. Cancer **39**:1-24 (May) 1940.

2. Tumours retain, in great measure at least, the genetic specificity of the individual in which they originate. . . .

3. Tumours retain to a variable extent the properties of the particular tissue from which they originate.

4. Each tumour has specific properties; tumours owning the same parent tissue have family resemblances but individual peculiarities.

5. All these properties are permanent and hereditary. . . .

6. The process of conversion of normal into tumour cells is irreversible.

Tumors arise, Foulds continued, from adult cells, and their structure and behavior are determined by anaplasia, not by "embryonal" qualities. Embryonal normal cells do not behave as cancer cells. The cell "rest" hypothesis, as an important source of cancer, is discredited.

Attempts to establish fundamental differences between normal and cancerous cells of the same type, Cowdry [2] said, have failed to bring out any striking variation in chemical makeup, enzyme content, metabolism or structure. Differences are qualitative. Neither normal nor cancerous cells are uniform in properties. He stated:

Both go through periods of youthful vigor, maturity and old age, ending in death. To compare young epidermal cells, capable of multiplication, with keratinizing cells in a squamous cell carcinoma . . . would be misleading. Selection of corresponding periods in the life cycles of both is difficult, but it should be attempted. . . .

Malignant cells are seldom uniform in their properties throughout a tumor. The cells in some areas may be proliferating rapidly, while those in others may be undergoing [varieties] of degeneration. . . .

Both malignant and normal cells may die quickly or slowly. . . . Tumor cells, according to Ewing (1940), "suffer the same degenerative changes as normal tissue." . . . Cells [of normal tissues] may die in orderly strata, as in the epidermis in consequence of progressively increasing deprivation of vital necessities. . . .

Some epithelial cells discharge their allotted function by dying in the right way—they keratinize. Malignant cells of the same lineage may also keratinize, though perhaps not in quite the same fashion.

The cell is the unit of cancerous tissue as of normal tissue, Strong [4] observed, and he pointed out that inoculation of cancerous tissue is a transplantation and not an infection and that, furthermore, uniform behavior of a tumor implies a relatively stable mechanism for its perpetuation.

It is with this background that I approach the interpretation of histologic evidence, conscious of the fact that histologic preparations are two dimensional, preserved and dyed pieces of dead stuff in which movement and growth do not exist but from which one can plausibly infer what might happen if the tissue were three dimensional and alive.

4. Strong, L. C.: General Considerations on the Genetic Study of Cancer, J. Cancer Research **10**:219-228 (July) 1926.

Histologists are not always so careful in their epistemology. They are likely to infer that "situation beneath" implies "downgrowth from" or that "adjacence to" implies "derivation from." Yet it is recognized [5] nowadays that the epidermis in Paget's disease of the nipple actually exemplifies "admixture with," abnormal cells being intermingled with normal ones without losing their cancerous identity, as peas and beans might be mixed in a sack. All of one kind retain their genetic relations with one another and their distinction from those of the other kind. The illustrations of Muir,[5] especially his figures 11, 12, 13 and 14, show isolated cancer cells disseminated throughout the epidermis, groups of the same kind of cells adjacent to the epidermis and large groups of cancer cells within the epidermis. What has been called "dyskeratosis"—as inexplicit a word as ever a morphologist conjured up—is now known, in Paget's disease, to signify the disrupted state of the epidermis due to the coexistence of two kinds of cells in it. When the morphologist asks, "What name can be applied to this configuration of things?", with regard to Paget's disease he answers, "The phenomena are dyskeratotic." When one asks, "What's going on here?", with regard to Paget's disease one answers, "Cancer cells are living among normal ones, disrupting their normal relations." My point of view is, "What's going on here?"

## DEFINITIONS

By "normal epithelium" I mean the entire normal epidermis and its accessory structures. "Epidermis" refers to the outermost epithelial covering of the skin, and it may be composed of either normal or neoplastic epithelium. "Derivation from" refers to such alterations as cornification in which normal corneum derives from normal epithelium and likewise abnormal corneum derives from neoplastic epithelium. "Epithelium of one kind" refers to the basal layer, the spinous cells derived from it and the dead, keratinized cells derived from them. Neoplastic epithelium, too, is of one kind, and in it, as in normal epithelium, are young cells, old cells, mitotic cells and dead, keratinized cells. By "intergradient transition" I mean that kind of continuous change whereby basal cells become malpighian layer cells and ultimately corneum cells. By "adjunction" of two kinds of epithelium I mean the relation seen in figure 1, where epitheliums not of the same kind are adjacent. With these definitions, I proceed to a consideration of the problem of whether neoplastic and normal epitheliums in epithelioma of the skin are of one kind, intergradient at any or all points where they adjoin, or are of two kinds, adjoined or perhaps intermingled.

5. Muir, R.: Further Observations on Paget's Disease of the Nipple, J. Path. & Bact. **49**:299-312 (Sept.) 1939.

ADJUNCTION OF TWO KINDS OF EPITHELIUM

Goodpasture, Douglas and Anderson [6] reported their successful transplantations of thin bits of human skin onto chick embryos, the human tissue being laid aseptically on the chorioallantois, where in most cases it adhered and lived. The embryos sustained such growth for eight days or more, the incubation period of the egg totaling twenty-one days. These authors described their observations as follows:

> One of the most interesting phenomena in connection with a skin graft on the membrane is the perfect approximation of the ectodermal epithelium of the membrane with that of the piece of skin at its periphery. The fusion is so exact and the union so nearly perfect that it would be difficult to detect it, did the smaller chick epithelial cells not take a lighter stain. In some preparations it appears that the two types of epithelium are laced together by cellular fibrils which pass between them, producing intercellular bridges or prickles. One gains the impression of an affinity or positive chemotaxis between the epithelium of the host and that of the cut edge of the graft.
>
> On the other hand an opposite relationship seems to exist between the mesodermal tissue of the corium of the graft and the ectoderm of the membrane. In the presence of the graft the latter tends to disappear from beneath or to aggregate in small foci where it assumes the appearance eventually of epithelial pearls.
>
> In the case of skin grafts from an old man over 70 years of age the cells of such epithelial pearls underwent rapid multiplication with extensive keratinization so that fairly large dermoid cysts were formed. Our observations of this are too limited to draw definite conclusions, but it is suggested that hyperkeratosis of the graft may influence keratosis of membranal ectoderm.
>
> The exact mechanism by which membranal ectoderm disappears or draws apart in the presence of skin grafts has not been determined. It is of interest, however, that mesodermal grafts (i. e. of muscle, spleen and cartilage) rapidly sink into the mesoderm of the membrane and the ectodermal layer becomes completely restored and reunited over them.
>
> The observation was made that skin grafts from two human cadavers also tended to sink into the mesoderm of the membrane, but apparently were prevented from becoming completely incorporated, by a union of the epithelial edges with the ectoderm of the host.
>
> Two skin grafts implanted on the same membrane with edges only a few millimeters apart have shown no tendency of the human epithelium to grow over the gap in a period of a week. As in single grafts the epithelial margins were sealed by the fusion with them of the ectoderm of the membrane.

To obtain a view of known adjunction of two kinds of epithelium, I examined sections of grafts of human tissues onto the chorioallantois of chick embryos, loaned by Dr. E. W. Goodpasture.

Figure 1 shows grafts of human skin onto the chorioallantois of chick embryos. *1* shows two five day grafts onto one embryo; *a* indicates the junction

6. Goodpasture, E. W.; Douglas, B., and Anderson, K.: A Study of Human Skin Grafted upon the Chorio-Allantois of Chick Embryos, J. Exper. Med. **68**:891-904 (Dec.) 1938.

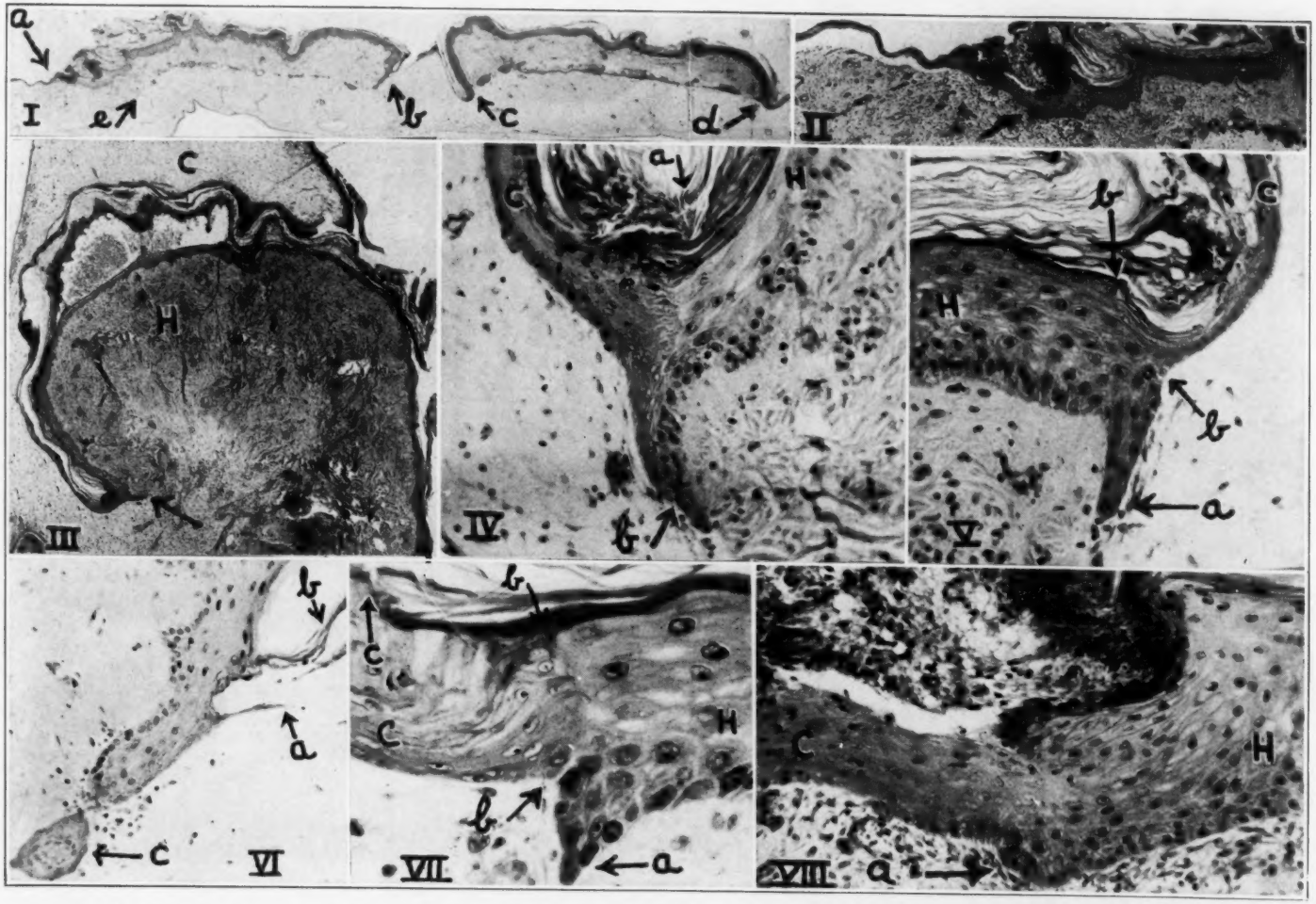


Fig. 1.—Grafts of human skin growing on chick chorioallantois (Dr. E. W. Goodpasture), showing conjunction of two different kinds of epithelium.

of chick epidermis with human epidermis, this junction being depicted in *II* and, at high magnification, in *VIII; b* indicates fusion, highly magnified in *VI; c* indicates aggregation in small foci of chick epithelium on which the human tissue was laid. *III* shows a nine day graft; the arrow indicates fusion, which is shown at high magnification in *IV; C* indicates chick tissue and *H* human tissue which is surviving and healthy. *IV* shows fusion, indicated in *III;* note the differences between epitheliums which were alive and also between corneums which were derived from these two kinds of fused and juxtaposed epitheliums; *a* points to fusion of corneums and *b* to fusion of strata mucosa; note that the growth of the basal cell layers has pushed downward tongues of abutting epithelium of both kinds. *V* shows the fusion indicated by *d* in *I; a* indicates a tongue of human epithelium stretched inward to attach with deteriorated aggregates of chick epithelium underlying the human tissue; "balled-up" chick epithelium has undergone spontaneous degeneration, and its union with the tongue of human cells *a* has deteriorated, just as its own continuity, as seen in *I e*, has deteriorated; *b* indicates the fusion line of chick and human epitheliums. *VI* shows fusion (*I b*); here the chick epithelium is feeble, broken and discontinuous; *a* indicates atrophic chick tissue and *b* human corneum torn from human epidermis; from *a* a strand of chick tissue fused with human tissue stretches to a ball *c* wholly of chick epithelium lying under the graft. *VII* shows *I c* at high magnification (compare *VII a* with *V a* and *VII b* with *V b*); human corneum extends far to the left, distorting the superficial cells of chick epithelium; examination of physical relations at *I c* shows why this should be so; broken fusion of corneums at *VII c* corresponds to *IV a*. *VIII* shows at high magnification the fusion seen at *I a; a* indicates a proliferation of human cells bulging around the blunt end of the chick epidermis.

Fig. 1.—Grafts of human skin growing on chick chorioallantois (Dr. E. W. Goodpasture), showing conjunction of two different kinds of epithelium.

Good illustrations of simple adjacence of cancer tissue to normal are seen in the paper of Lucké and Schlumberger,[7] who transplanted tissue from a renal carcinoma of the frog into the anterior chamber of the eye. Their figures 9 and 11 show spread of the tumor in a single layer of cells over the lens capsule, overlying normal epithelium. Their figure 10 shows adjacence of tumor tissue to the corneal tissue. The homogeneous strain of cancer cells looks considerably different when the cells are arranged in single layers and when they grow loosely in acinar formations.

## HISTOLOGIC ANALYSIS OF ELEVEN SPONTANEOUS HUMAN TUMORS

SPECIMEN 1 (tumor 87; fig. 2, *I, II* and *III*).—A hornlike squamous cell epithelioma was taken from the helix of a white man 87 years old. Several acanthotic nevi and senile keratoses were also present on the exposed skin of the patient, who had a fair complexion and blue eyes and lived an outdoor life. The pointed horn of this tumor arose 1.5 cm. from a firm hemispherical base attached by a wide pedicle. The lesion developed from a "pimple" noted six months previous to its excision.

7. Lucké, B., and Schlumberger, H.: The Manner of Growth of Frog Carcinoma Studied by Direct Microscopic Examination of Living Intraocular Transplants, J. Exper. Med. **70**:257-268 (Sept.) 1939.

In figure 2, *I* shows a whole tumor section of this lesion. As one follows the normal epithelium from the pedicle left to the indicated rectangle, the character of the epidermis appears unchanged until the zone shown in detail in *II* is reached.

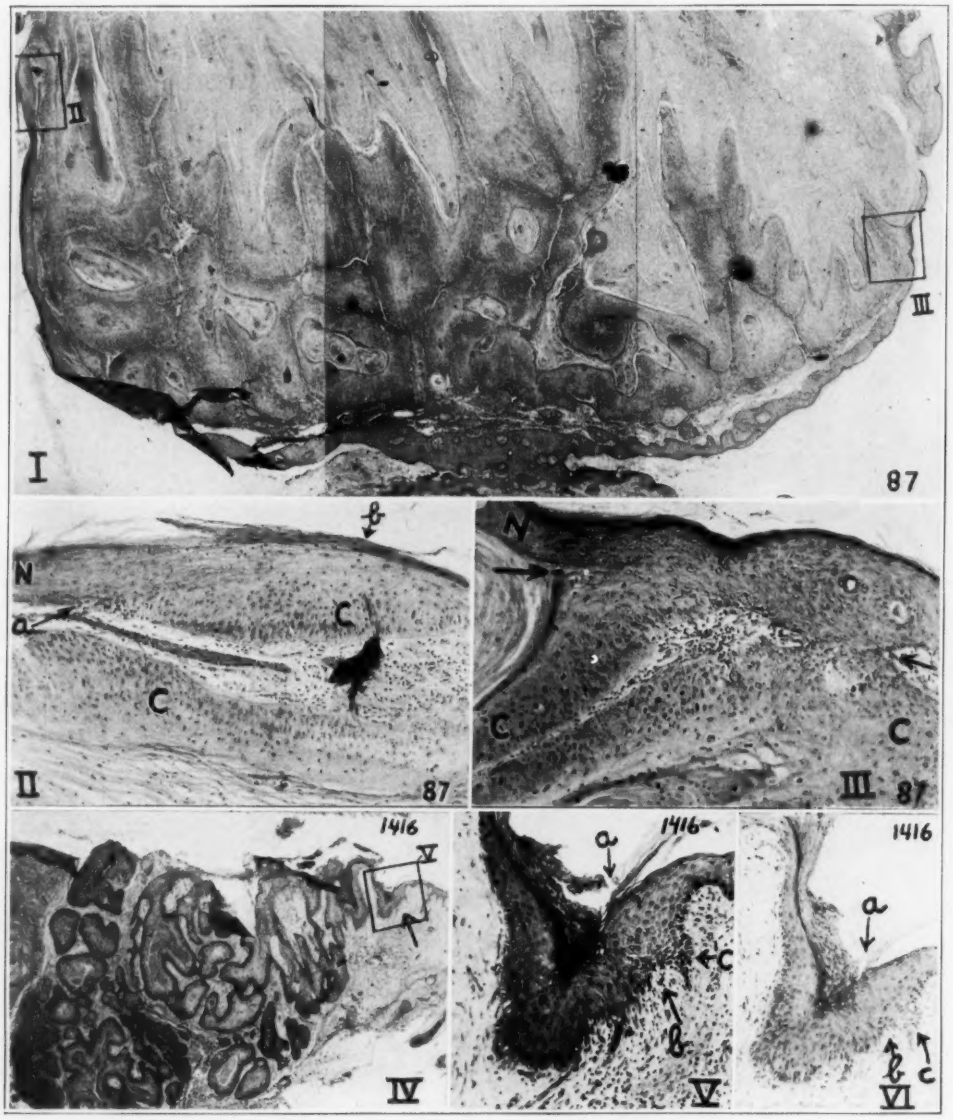


Fig. 2.—*I*, *II* and *III*, specimen 1 (tumor 87), from the ear. *IV*, *V*, and *VI*, specimen 2 (tumor 1416), from the scalp.

Similarly, if one follows the normal epithelium from the pedicle right to the indicated rectangle, the character of the epidermis is unchanged until the zone shown in *III* is reached. *II* shows the junction zone of normal *N* with carcinoma-

tous epithelium *C*, showing abrupt, sloping transition; *a* indicates the line of fusion, which is not perpendicular; carcinomatous epithelium apparently undergrew the normal here; *b* points to parakeratotic corneum derived by intergradient transition from normal epithelium. *III* shows fusion of carcinomatous epithelium (*C*) in stratified bands of cells with normal epithelium (*N*).

Specimen 2 (tumor 1416; fig. 2, *IV*, *V* and *VI*).—The lesion came from the scalp of a white woman 65 years old. It was a crusted intracutaneous nodule, about 8 mm. in diameter, set within the scar resulting from surgical removal of a tumor from this site four years previously. The clinical diagnosis was recurrence of basal cell epithelioma. The final diagnosis was stratified squamous cell epithelioma of slow growth rate.

In figure 2, *IV* shows a whole tumor section of this lesion; the arrow indicates the zone where transition from tumor cell epidermis to normal epidermis was found. *V* shows at *a* the abrupt alteration from stratified tumor cell epidermis to normal epidermis; *c* points to a tongue of normal basal cell proliferation, comparable to *VII a* and to *VIII a* in figure 1. *VI* shows the same region as *V*, photographed from another section of the same tumor; *a*, *b* and *c* are as in *V*.

Specimen 3 (tumor 542; fig. 3).—A warty nodule was removed from the cheek of a farmer.

In figure 3, *I* shows the whole tumor section at low magnification. *II* shows the left margin of the tumor; following the normal epidermis from left to right, one notes at *a* that normal epidermis has become acanthotic and hyperkeratotic, for it rests on inflamed dermis which is infiltrated with stratified bands of tumor epithelium; normal epithelium provides the epidermis of all the region shown in *II*. *III* shows bands of tumor tissue applied against the underpart of the epidermis; at *a* tumor tissue terminates; at *b* normal epidermis is represented only by corneum, for tumor epithelium has supplanted the normal almost completely. *IV* shows the right margin of the tumor; the only normal epithelium visible is at *a*, where part of the wall of the large fat gland duct is seen; *b* indicates corneum derived from tumor epithelium, for the epidermis along the top of *IV* is tumor epithelium, which cornifies with retention of nuclei and with greater cohesiveness than the normal corneum, seen at *a*. Note in *IV* that the whole surface is cancerous.[8] One cannot say that there is downgrowth of cancer "from" the epidermis; the epidermis here and the epithelioma are one; compare with figure 7 *V*.

*V* shows undermining of the normal epithelium by a tongue of tumor tissue. *VI* shows part of *V*, and *a* indicates the line of fusion; note parakeratosis of the tumor corneum *c* in contrast with the absence of nuclei in the corneum derived by intergradient transition from normal epithelium *b*. Note the slope of this line of fusion, for it serves as a time chart: when the corneous cells at *a* were alive, living normal epithelium extended to that upward distance, while now normal corneum is developing at *b*. This slope supplies positive evidence of direction of progress; movement is not visible in a histologic preparation, yet one knows

8. Warwick, M.: Model of Carcinoma of the Lip Reconstructed from Serial Section, J. A. M. A. **82**:1119-1120 (April 5) 1924. [She made this error, writing: "This epithelial growth arises . . . from numerous papillary projections arising from multiple points in the surface epithelium and separated by epithelium which is normal in appearance."]

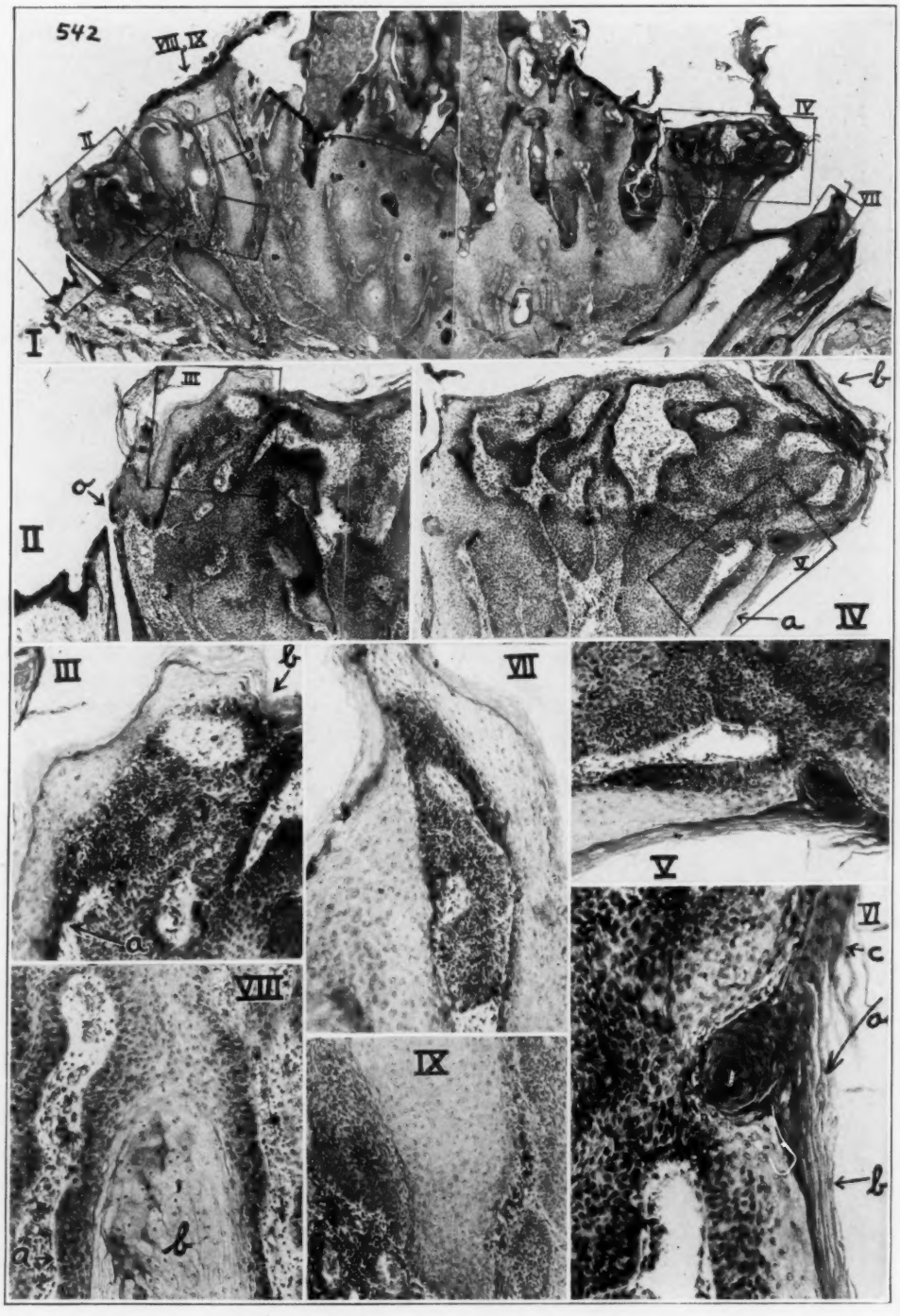


Fig. 3.—Specimen 3 (tumor 542), from the cheek.

that, since the slope is as it is, the tumor tissue must actually have been progressively displacing normal tisue. *VII* shows the right side of the large fat gland duct shown in *I*. A band of stratified tumor epithelium has wedged its way around the tubular duct, shoving along at the dermoepidermal junction just as it shoved its way beneath the epidermis, as shown in *V* and also at *III a*. The dermoepidermal junction is apparently a line of least resistance.

*VIII* and *IX* show the upper and lower parts of a follicle composed of normal epithelium engulfed almost completely by tumor epithelium. As tumor epithelium pushed along the dermoepidermal junction, it externalized normal basal cells from their nutrient supply. Basal cells ceased to be basal cells and lost their palisade arrangement. Basal cells are the same kind of cells as the externally located daughter cells which, derived from them, comprise stratum mucosum. Basal cells differ from stratum mucosum cells only in location and environment. When basal cells are pushed into the location and environment of stratum mucosum cells, then they are stratum mucosum cells. Thus, one sees at *VIII a* that tumor cells are basal cells while normal cells *b* are decadent. In *VIII* no keratinized cells are seen to be derived from tumor cells; the sharp distinction of two kinds of cells persists; *b* indicates a horny pearl composed of dead normal cells. In *IX* the normal cells are not dead as yet, but they are progressively being surrounded by stratified bands of tumor tissue.

Specimen 4 (tumor 1187; fig. 4).—A scaling, slightly indurated and inflamed "keratosis," 1 cm. in diameter, of several years' duration, was removed from the cheek of a man 49 years of age, a highway engineer, whose eyes were blue, hair sandy, skin fair and face spotted with other keratoses.

In figure 4 *I* shows a whole tumor section of the lesion. The left end shows blistering from the cautery. The right end is curtailed but extends to the termination of all traces of abnormality. Abnormality consists in folds and strands of extra epithelium at the dermoepidermal junction, along with inflammation. *II* shows a strand of epithelium which does not resemble adjacent normal epithelium yet looks to be of one kind, homogeneous within itself; at *a* it terminates; three dimensionally the strand must be a sheet. *III* shows part of *II*; *N* indicates normal epithelium, *C* the different kind of epithelium and *a* the intercellular junction between *C* and *N*. *C* is not derived from *N*; all of *C* is one kind of cells, and all of *N* is another kind. *IV* shows the left side of the sebaceous follicle of which *II* shows the right. At *a* the strand terminates as at *III a*. From *b* to *c* normal corneum has been undergrown by tumor cells which have replaced those of the normal stratum mucosum. At *b* tumor cells seem to have wedged into the stratum mucosum, while at *c* and to the right of *c* they form a fold and extend as a sheet at the dermoepidermal junction. There is clear juxtaposition of two kinds of epithelium, but there seems no question of the one being derived from the other. *V* shows at *a* a termination comparable to *III a* and to *IV a*. From *b* to *c* normal stratum mucosum has been replaced, just as in *IV* from *b* to *c*. From *c* to *d* the epidermis is composed of tumor cells for the most part, though there is some commingling of normal with abnormal near *c*, as in Bowen's disease.[9] From *c* to *d* corneum derived from abnormal cells appears different from corneum derived from normal cells. From *d* toward *a* one sees supplanting and undermining of normal by abnormal cells. In my interpretation, two kinds of cells are present. An alternative interpretation might

9. Cipollaro, A. C., and Foster, P. D.: Bowen's Precancerous Dermatosis of the Mucous Membrane, New York State J. Med. **40**:264-275 (Feb. 15) 1940.

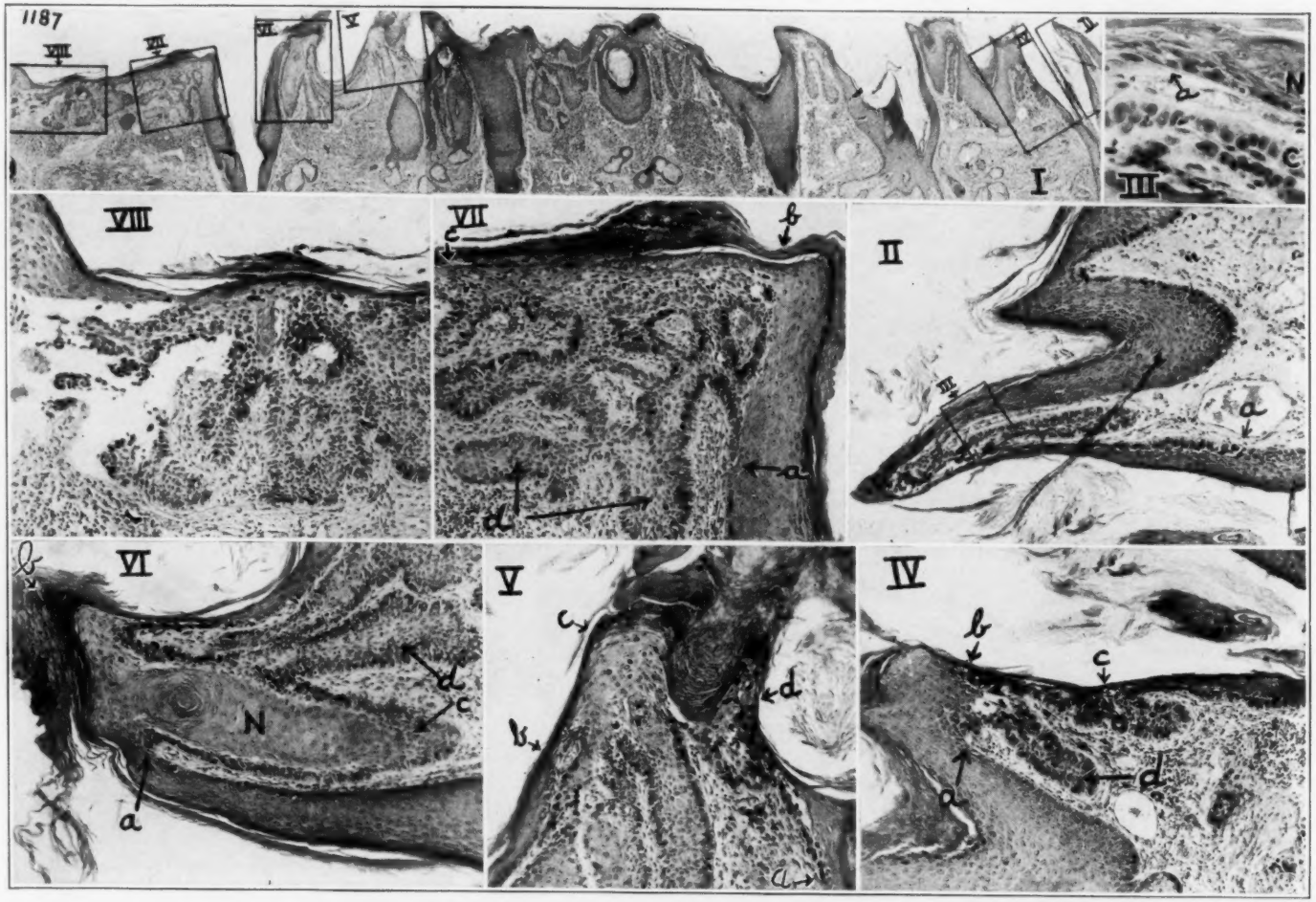


Fig. 4.—Specimen 4 (tumor 1187), from the face.

postulate derivation of abnormal cells from normal in the region of *c;* such a hypothesis seems untenable in consideration of the whole tumor. *VI* shows at *a* a termination like *III a, IV a* and *V a.* The corneum between the two follicular orifices is derived from mingled normal and tumor cells. *b* points to the fusion line between normal and abnormal corneum. *c* indicates the abnormal cells ensheathing the normal ones (*N*) and cut obliquely; compare with *IX* in figure 3. *d* indicates a stratified mass of tumor cells derived by proliferation of a folded sheet, analogous to *IV d. VII* shows at *a* a termination like *IV a.* From *b* to *c* the epidermis is composed of mingled tumor cells and normal cells, simulating Bowen's disease. The corneum derived from the mixture is not homogeneous, being in part parakeratotic. *d* indicates proliferating masses of tumor cells like *VI d. VIII* shows masses of tumor cells underlying and almost completely replacing normal stratum mucosum. At the left is distortion due to burning. The evidence points to incompleteness of extirpation of all tumor tissue. I do not know whether recurrence has occurred.

Specimen 5 (tumor 143; fig. 5).—A raised, indurated nodule, 2 by 3 cm. in diameter, with a central crust, was removed from the left maxillary area of a 47 year old farmer with dark hair, gray eyes and sun-sensitive skin. It had developed in the previous two years from a "scaly patch."

In figure 5, *I* shows the left marginal portion of a whole tumor section. Ulcerative epithelioma extends from *a* to *b* and beyond *b.* The subepidermal region of apparently normal skin left from *a* is of interest. The fat glands are of normal size, and the surface is cornified normally. *II* shows the transition zone from normal epidermis to epitheliomatous epidermis. Note the thinning and fraying at the termination of the normal epithelium and the adenoid folds of cancer cells, many of which have keratinized, at *a;* these have formed a sheet undergrowing the normal epidermis as far as *b. c* indicates horny pearls composed of dead cancer cells. *d* calls attention to the juxtaposition of cancer cells, growing in sheets and folds, to the basal layers of follicle wall and fat gland; compare with *IV.* The transition zone in *II* (compare with fig. 8 *XI*) corresponds to what Brunschwig and Tschetter [10] showed in their figure 6; they titled their figure an illustration of cancerization showing a point where cancer cells were "streaming downward into the lesion." Their interpretation is not acceptable. In my figure 5, *II* shows the normal cells to be necrobiotic and doing anything but "streaming." *III* shows part of *II,* clarifying the relation of cancer cells in a folded sheet (*a*) undergrowing normal epidermis as far as *b,* which is a termination like *II a* in figure 4. *IV* shows cancer cells in little lobular aggregates and a sheet of cancer cells (*a*) assuming the relation of basal cell layer to the normal follicular epidermis (*b*). At *c* the sheath of cancer cells terminates as in *III b.* V shows at *a* fusion of the cancer cell layer with normal epidermis, but at *b* the undermining cancer cell layer is separated from normal cells by a cleft.

The space between the tumor cell sheet and the normal epidermis was accounted for, in figure 1 of my earlier article,[1] as an artefact representative of the relatively slight cohesion between the two kinds of cells and of their movement with respect to each other due to the expansion of the tumor cell

10. Brunschwig, A., and Tschetter, D.: The Mode of Inception and Lateral Spread of Certain Squamous Cell Carcinomas: A Histopathologic and Experimental Study, Surg., Gynec. & Obst. **67**:715-721 (Dec.) 1938.

Fig. 4.—Specimen 4 (tumor 1187), from the face.

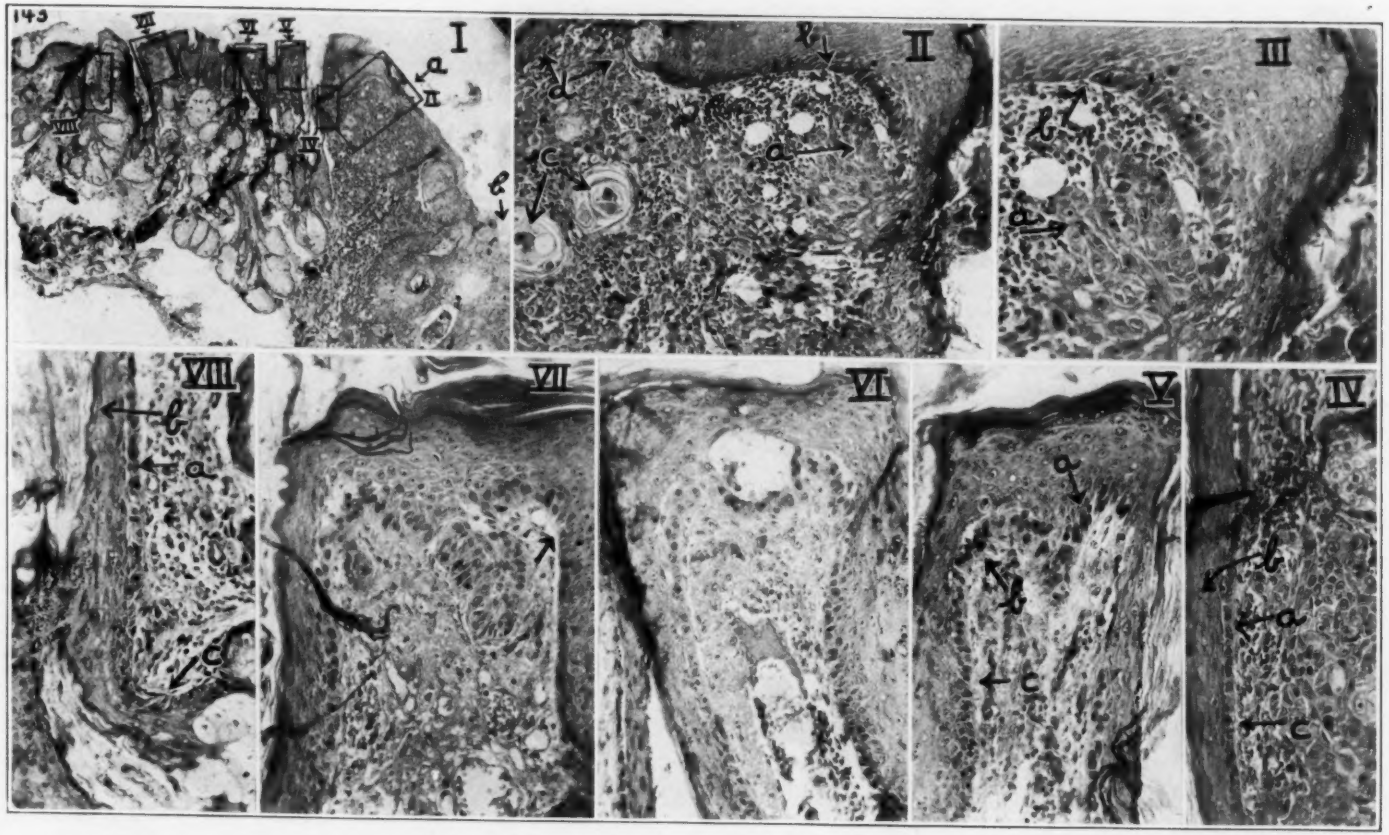


Fig. 5.—Specimen 5 (tumor 143), from the face.

sheet. Expansion gives rise to shearing stress. Where shearing stress is not present, no such artefact exists. I showed why I am sure that tumor tissue proliferates faster than normal in the description of *V* and *VI* in figure 3. There is no "dropping down" of normal cells from the basal layer, as has been hypothesized. Study of figures 294, 295 and 296 in "Introduction to Dermatology"[11] and of figure 5 in this report makes untenable such an explanation. In figure 5, *V c* is the sort of termination seen at *III b* and *IV c*. *VI* and *VII* show that the same phenomena seen in *V* extend to a surprisingly considerable distance from the intramesodermal mass of the tumor. In *VII* the arrow points to termination like *III b*. *VIII* shows a sheath of cancer cells (*a*) extending deep along the dermoepidermal junction of the normal epithelial wall (*b*) of a fat gland duct, as in *IV a*, and *c* indicates the termination of cancer cell spread.

SPECIMEN 6 (tumor 128, fig. 6).—A hemispherical, crusted, sessile, warty lesion, 1 cm. in diameter, was removed from the helix of the left ear of a blue-eyed, fair-skinned farmer 75 years old. It was not fixed to the perichondrium. It had developed in six months from a scaly, thorny "pimple." Three other cutaneous epitheliomas were removed from this patient at various times.

In figure 6, *I* shows a whole tumor section of this lesion; at the extreme left and right are normal large sebaceous glands. *II* shows the right margin of this tumor. That which is epitheliomatous (*C*) and that which is not (*N*) are clear, but at *a* this section is folded. Therefore the corresponding part of another section is shown in *IV*. Note in *IV* the Bowen's disease type of mingling of tumor cells and normal ones; where corneum is derived from tumor cells, it is parakeratotic. *III* and *V* show parts of *II*, clarifying the nature of the basal cell layer of the epidermis, here seen to be normal though active. *VI* shows the left margin of the tumor; at *a* all epidermal tissue is of tumor cell origin. The juxtaposition of tumor cells and normal ones is apparent, while at and perpendicularly external to *b* there is some admixture, as seen in *IV;* at *c* there is fusion, and at *d* there is undermining of the normal tissue by a folding sheet of tumor cells. No appearance as of derivation of tumor tissue from normal tissue is seen here or in *II*. *VII* shows a folded band of tumor cells, lying external to my row of dots, beneath the normal epidermis, in places fused and in others separated by a cleft like that seen in figure 5 (*V b*). *VIII* shows the deep part of a follicle, distorted and damaged by being surrounded by tumor cells. Fusion is seen at *d*, and mingling is seen at *b*. No derivation of *C* from *N* can be hypothesized here or in *VII*. *IX* shows pseudoepitheliomatous hyperplasia[12] of sebaceous follicle epithelium (*N*), contrasted with *X*, which shows pure epithelioma (*C*). *XI* shows the deep end of a follicle retaining a few sebaceous cells despite its curtailment and compression by the surrounding cancer tissue.

SPECIMEN 7 (tumor 355; fig. 7).—A well developed epithelioma was taken from a man's lower lip. The neck glands were not palpable, and six years after the cautery excision of the lesion the patient remained cured.

In figure 7 *I* and *II* show respectively the right and left edges of the tumor as seen in one whole tumor section. *III* shows part of *I*, *N* indicating normal epithelium extending deep beside cancerous tissue (*C*). Cancer tissue (*C*) abuts

11. Sutton, R. L., and Sutton, R. L., Jr.: Introduction to Dermatology, ed. 4, St. Louis, C. V. Mosby Company, 1941, p. 400, fig. 315, bottom.

12. Winer, L. H.: Pseudoepitheliomatous Hyperplasia, Arch. Dermat. & Syph. **42**:856-867 (Nov.) 1940.

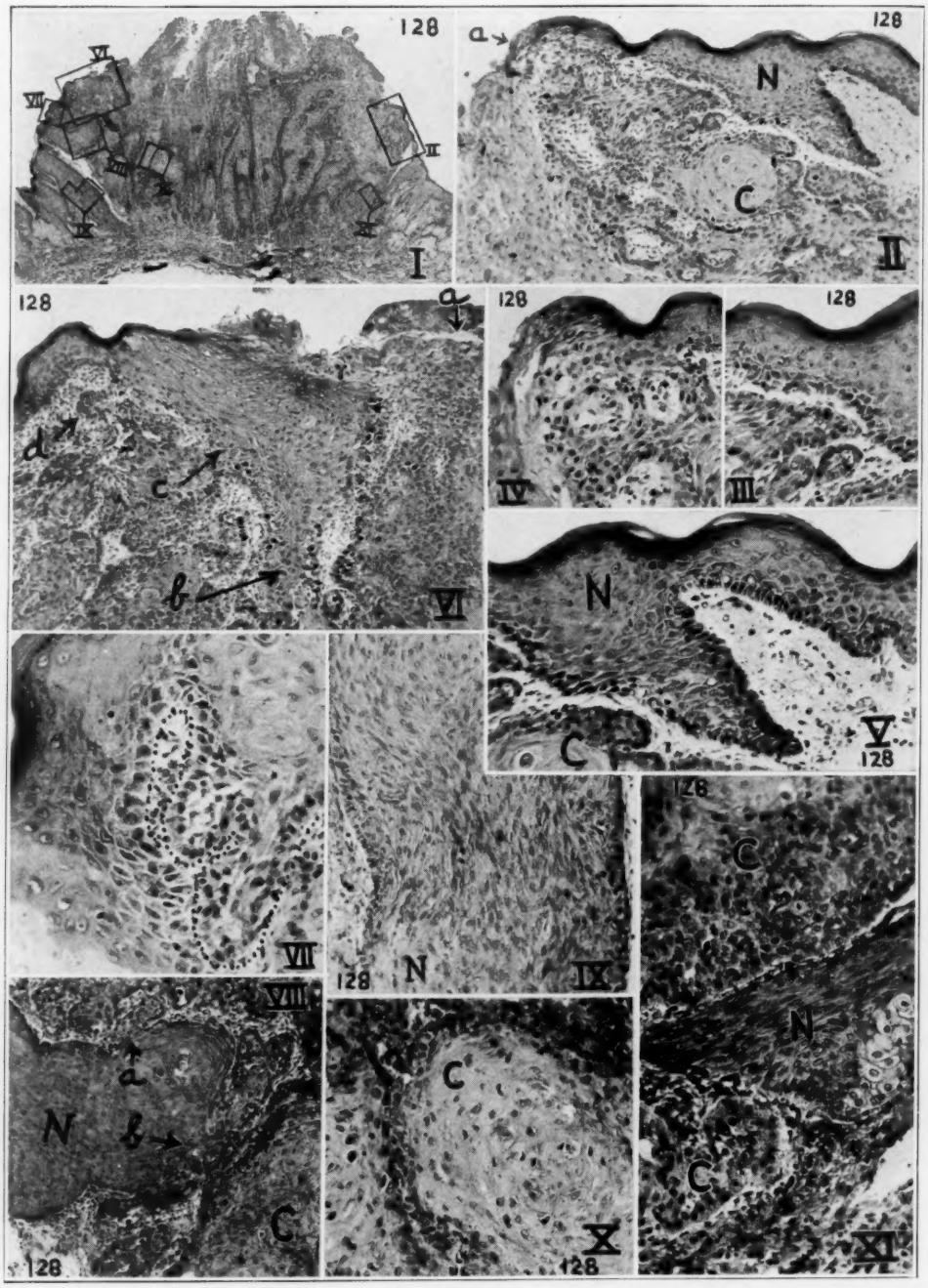


Fig. 6.—Specimen 6 (tumor 128), from the ear.

normal (*N*), and from *a* to *b* cancerous corneum is fused with normal corneum (compare with *VI*), but there is no question of derivation of one from the other. Compare with *II* in figure 3, which also shows a carcinoma in which cancer

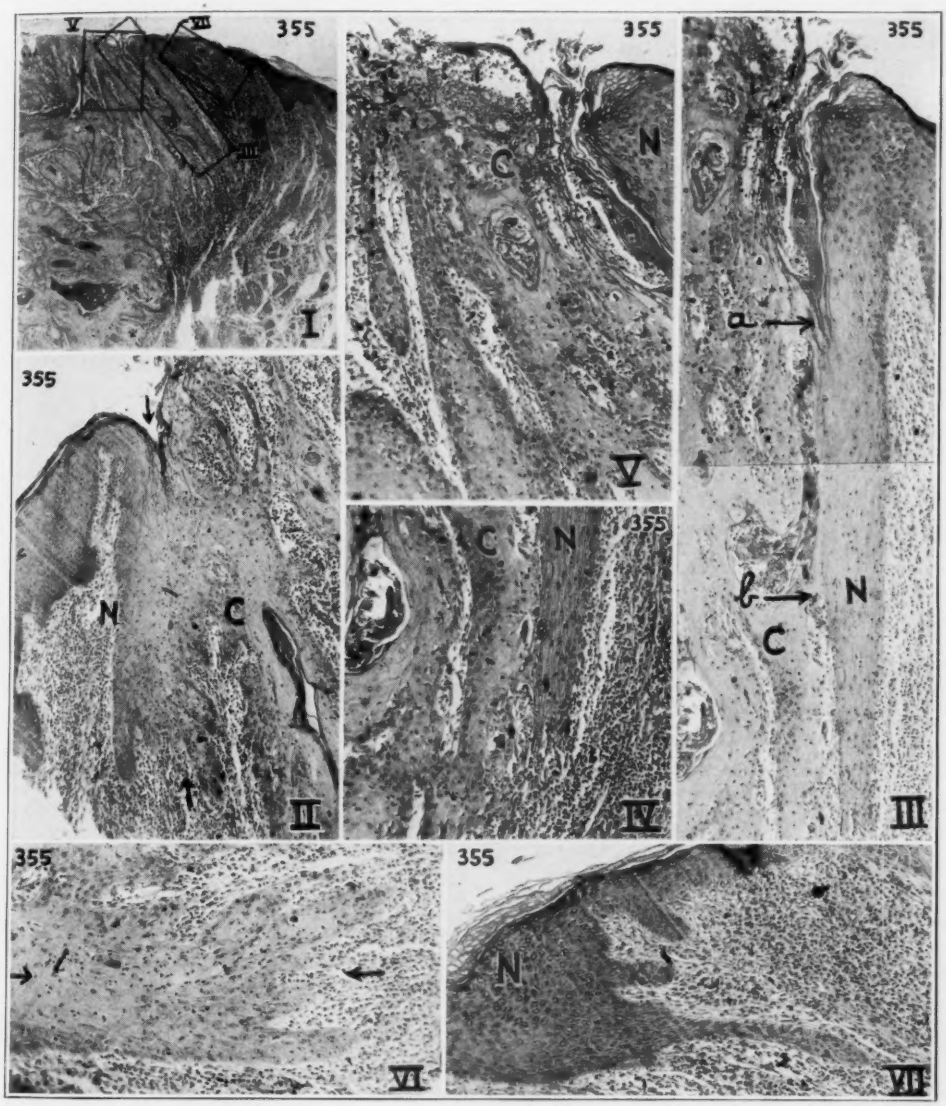


Fig. 7.—Specimen 7 (tumor 355), from the lower lip.

cells form stratified bands. *IV* shows the deep termination of the hyperplastic tongue of normal epithelium seen in *III*. In *V* one sees the sharp distinction between normal epidermis (*N*) and such epidermis (*C*) as cancer tissue provides.[8] In *II* one sees the normal epithelium (*N*) dipping deeply into the mesoderm (as in *III*) but fused with tumor tissue (*C*) in such a fashion that visual

examination does not certainly distinguish normal from cancerous tissue. In my opinion, a line joining the two arrows indicates the line of fusion. *VI* shows the equivocal terminal region, counterpart of *IV*, where fusion has occurred. Again, a line joining the two arrows indicates, I believe, the line of fusion. Compare with the fusion line between *a* and *b* in *III*. *VII* shows a part of *I*, where pseudoepitheliomatous hyperplasia [12] stimulates epithelioma.

SPECIMEN 8 (tumor 237; fig. 8, *I* to *IV*).—A flat, firm, button-like disk was located on the central mucosal part of the lower lip of a fair-skinned, blue-eyed farmer 63 years old. When a crust was wiped from the surface of the nodule, a granular oozing base was revealed, which with a translucent pearly peripheral zone comprised the lesion, 1 cm. in diameter. It had developed in one year from a scaly patch at the site where the patient habitually held a cigaret. No gland was palpable at the time of operation, but nine months later the patient had a huge submaxillary lymph gland metastasis. He died.

In figure 8, *I* shows the left side of the whole tumor section. *II* shows part of *I*, revealing squamous cell structure. *III* shows the transition zone of *I*, where *p* indicates pseudoepitheliomatous hyperplasia [12] of normal epithelium, *C* indicates epithelioma and *c* indicates corneum derived from cancer cells, which comprise all the epidermis, such as it is, lying to the right of *a*. *IV* shows the same region of another section, similarly marked. This tumor could be diagnosed Bowen's disease [9] which has advanced to squamous cell epithelioma of grade 3. The distinction of cancerous cells from normal cells is perfectly sharp. No derivation of one from the other can be postulated.

SPECIMEN 9 (tumor 1510; fig. 8, *V* to *IX*).—A firm, crusted tumor, 4 by 5 mm. in size, was removed from the bridge of the nose of a farmer 69 years old, who had blue eyes, gray hair and numerous keratoses on his face. It had developed rapidly in the past three months.

In figure 8, *V a* indicates the junction zone of normal and tumor tissue, seen at high magnification in *VII*. To the left of *a* and to the right of *b* no further tumor cells exist. At *c* the tissue is torn. From *a* to *c* no normal epidermis remains. *VI* shows a subepidermal mass of cancerous tissue, separated from the main mass by a few hundred microns. A few tumor cells are mingled with the normal ones of the epidermis, but the corneum is normal; therefore this bit of tumor has not been fused with the epidermis for many days. *IX* shows the relation between the main tumor mass and this fragment. The available sections do not demonstrate continuity, but "multicentric origin" of clinically single lesions will be discussed in another part of the paper. *VII* shows the sharp line of demarcation between normal cells and tumor cells; at *a* the parakeratotic corneum is of tumor cell derivation, as it is also in *IX* from *a* to *b*. *VIII* shows the same region as *VII* in a different section. This lesion could be called the epitheliomatous progression of Bowen's disease. There is no question of derivation of abnormal from normal, for every visible epithelial cell can be classed as belonging to one of two kinds of cells.

SPECIMEN 10 (tumor 415; fig. 8, *X* and *XI*).—A man 42 years old had an advanced ulcerative recurrence of an epithelioma on the lower lip. He eventually died.

In figure 8, *X* shows one marginal zone. *P* indicates pseudoepitheliomatous hyperplasia [12] at the edge of the ulcer: *c* indicates surface composed solely of cancer tissue, and *a* indicates the termination of normal corneum beneath which

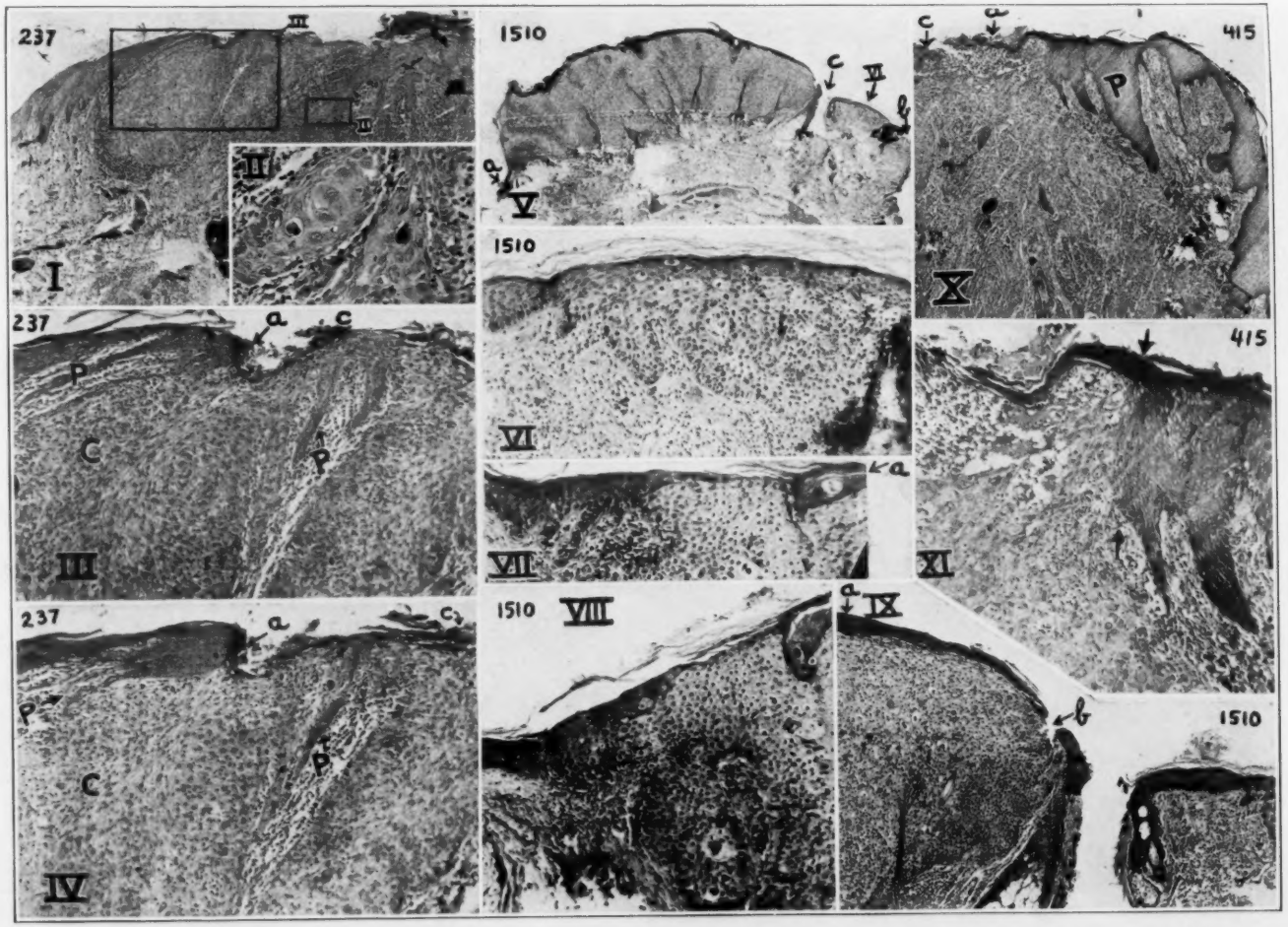


Fig. 8.—*I*, *II*, *III* and *IV*, specimen 8 (tumor 237), from the lip. *V*, *VI*, *VII* and *IX*, specimen 9 (tumor 1510) from the nose. *X* and *XI*, specimen 10 (tumor 415), from the lip.

the normal epidermis has been disrupted and displaced by cancer cells. In *XI* a sharp distinction is notable between the two kinds of tissue at their region of abutment. Since the lesion is a recurrent one, there is no problem of derivation, but the problem of "cancerization" of normal tissue [10] at the tumor margin is clearly answered. Compare figures 2, *V*, and 6, *VI*.

SPECIMEN 11 (tumor 829; fig. 9).—A shallow, crusted, sharply circumscribed, reddish, oozing lesion (fig. 9, *VII*), 2 by 2.5 cm. in size, was located on the temple at the hair line of a fair-skinned, sun-sensitive, 78 year old farmer, whose face supported many keratoses. It had been present three or four years and had slowly become more scaly, moist and troublesome.

In figure 9, *I* shows a section crossing the lesion from normal to normal; abnormality is limited to the epidermis and upper part of the dermis. *II* shows the left transition zone. Tumor tissue (*C*), obviously (in my opinion) basal cell in type, forms the whole epidermis at *a*, lies under normal corneum at *b* and undermines and abuts normal stratum mucosum as far as *c*. *III* shows the right transition zone, where normal stratum mucosum (*N*), followed from right to left, is thinned by encroachment of tumor cells that have slowly wedged in peripherad (compare with *V* in figure 3). *III a* (inset) shows normal prickle cells underlaid by tumor cells lacking intercellular bridges. *IV* shows the junction of neoplastic epidermis with normal sebaceous follicle, where tumor cells encroach. *V* shows much the same situation as seen in *IV*, though encroachment is more advanced. *VI* shows normal epidermis outside the tumor.

## INVASIVENESS OF EPITHELIOMA

Invasiveness of epithelioma clearly bears some relation to the physical properties of the cells. If they do not stick together, they can more readily insinuate themselves between normal tissue elements and can more readily reach lymph glands. If they do stick together, they remain shallow for a long time, and daughter cells are lost by keratinization, scaling off the surface rather than producing viable progeny in favorable environment (Mottram's "wastage by keratinization" [13]).

The rate of ulceration, studied by Wilson,[14] was reported to vary with the grade of the tumor (Broder's grading), the lesions of low grade ulcerating slowly and those of higher grades ulcerating rapidly, excepting tumors of grade 4, which ulcerate slowly because they invade fast. I [1] wrote:

> The faster the rate of growth, the sooner downgrowth will occur. It is clinically true of early cutaneous carcinoma that the wider the surface extension before dermal invasion takes place, the more benign the lesion. . . . [Compare

13. Mottram, J. C.: On Correlation Between Malignancy and Rate of Growth in Tar Warts in Mice, Am. J. Cancer **22**:801-830 (Dec.) 1934; On Origin of Tar Tumors in Mice, Whether from Single Cells or Many Cells, J. Path. & Bact. **40**:407-414 (March) 1935.

14. Wilson, W. D.: Rate of Ulceration of Epitheliomas of the Skin and Lip, Arch. Dermat. & Syph. **41**:667-677 (April) 1940.

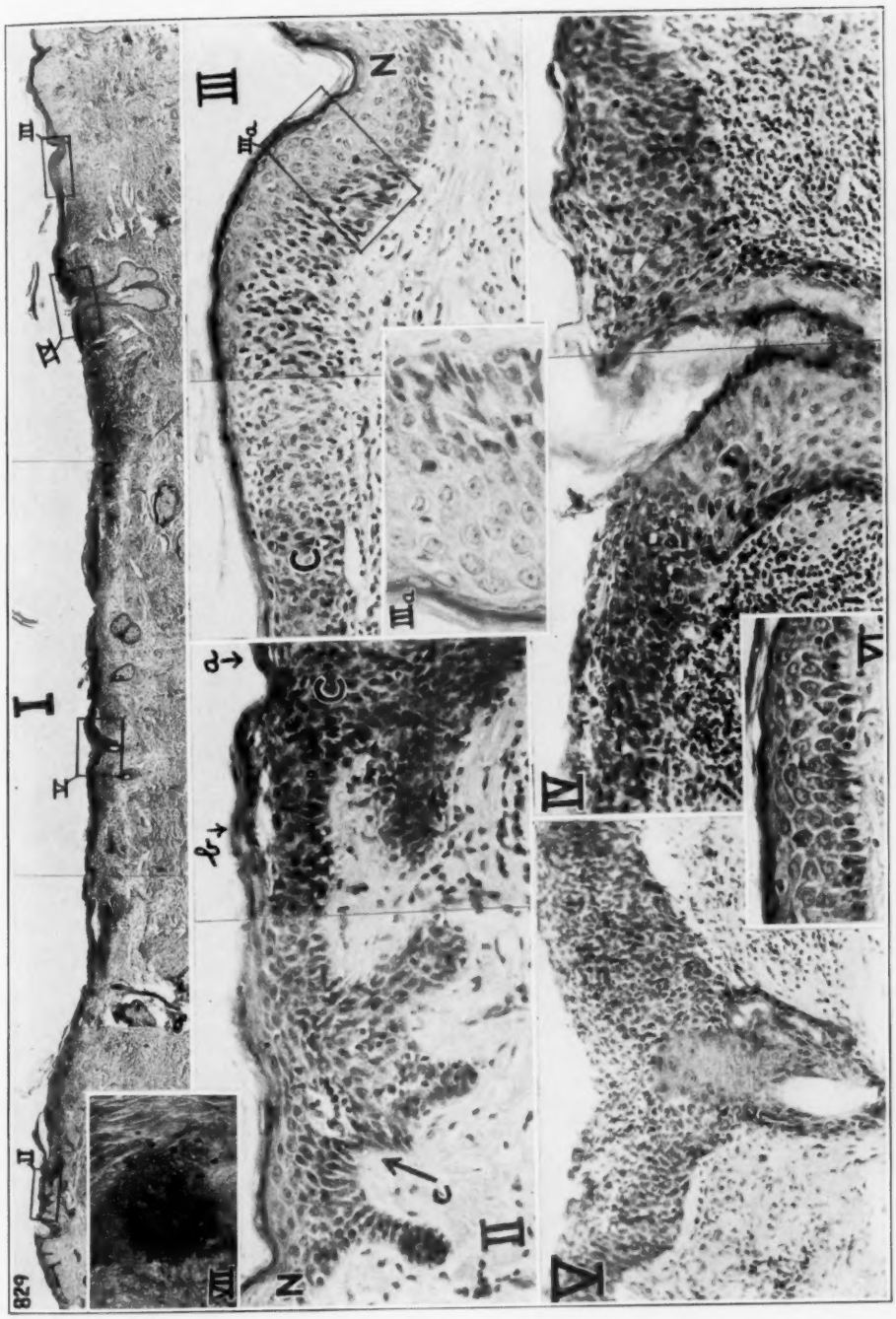


Fig. 9.—Specimen 11 (tumor 829), from the temple.

figure 6, showing a small, apparently malignant, squamous cell epithelioma which developed in six months, with figure 9, showing a far less dangerous, slower growing lesion.]

The growth of a colony of progeny of an altered cell may be practically without coherence. . . . If slow growing, the cells permeate the epidermis . . . as in Bowen's disease or Paget's disease of the skin. . . . If swiftly growing, the clumps of cells expand within the epidermis, soon bursting through the normal confines. . . . [Such] lesions . . . require only a short time to become obvious cancers. . . . Cells spread into the dermis in isolated units and clumps of small numbers. These correspond to Broders' most malignant class. In theory they should be—and in fact they are—most malignant, as judged by their readiness to metatasize. [Figure 8 presents good examples of the swiftly growing type.]

Invasiveness is somehow concerned with the inflammatory response of the mesodermal tissues. In general, the more intense the leukocytic reaction, the more malignant the lesion. Note the mildness of inflammation in figure 2, the relatively low intensity under the superficial basal cell lesion in figure 4 and the greater intensity in figure 7. Inflammation is associated with the presence of tumor cells, not necessarily with infection. In figure 9 the extent of mesodermal reaction delineates the extent of the tumor tissue. Perhaps leukocytic reaction is provoked by metabolites of tumor tissue. Doubtless some of it is due to foreign body reaction [15] to dead tumor cells, which are most intimately associated with reactive tissue in noncoherent lesions, as seen in figure 5, *II*. The quantity of irritant metabolites can be expected to be greatest in tumors whose cells grow most rapidly. But whether tumor growth incites leukocytic infiltration or leukocytic infiltration incites tumor growth is a question. In tissue culture experiments Ludford [16] observed that leukocytes stimulated the growth of fibroblasts whether they were in contact or merely nearby. He made the following suggestion: "Monocytes and macrophages by stimulating the growth and proteolytic activity of malignant cells may facilitate their invasive growth into normal tissues." Indeed, many an epithelioma has blossomed speedily from leukoplakia in which herpes simplex appeared, and herpetic inflammation is notable for its intense lymphocytic infiltration. There seems to be no doubt that succulent tissue infiltrated with leukocytes supplies good environment for invasion by cancer cells. I think that cancer cells simply grow where they can grow. Their activity promotes the development of an inflammatory dermis, which is a favorable environment, and into this they grow, provoking yet more inflammation. Parkhurst [17] found that the inflamma-

15. Hass, G. M.: Tissue Reactions to Natural Oils and Fractions Thereof, Arch. Path. **26**:956-965 (Nov.) 1938.

16. Ludford, R. J.: Interaction in Vitro of Fibroblasts and Sarcoma Cells with Leucocytes and Macrophages, Brit. M. J. **1**:201-205 (Feb. 10) 1940.

17. Parkhurst, A. J.: Tissue Reaction in Malignant Epitheliomas of the Skin, Arch. Dermat. & Syph. **6**:401-412 (Oct.) 1922.

tory infiltration seems to contain a higher proportion of plasma cells in slower growing lesions. One wonders to what extent the infiltration is a foreign body reaction to decadent epithelial cells, their keratinous detritus being the more profuse in proportion to the difficulty of their survival and reproduction. The stroma of the slowly growing, comparatively benign, calcifying epithelioma [18] is notable for its giant cells, which surround dead stratified epithelium.

Epithelium is a tissue which, as a conspicuous biologic attribute, possesses the property of covering surfaces on which it is capable of growing. When the surface is covered, continued growth—and normal epithelium does continue to grow throughout life—results in stratification, necrobiosis of distal cells and "wastage by keratinization." [13] Normal epithelium so behaves when it covers a granulating wound. If a new kind of epithelium possessed the property of provoking granulation tissue on which it could grow and of provoking mesodermal tissue which served it as an inhabitable surface, however folded, then the growth of this epithelium would be cancerous. The property of provoking such a surface deserves study. It is surely dependent on some chemical or metabolic difference from normal.

### MALIGNANCY, CLASSIFICATION, PROGNOSIS AND "PRECANCEROSIS"

Histologic classification of epitheliomas of the skin can be devised to take into account the properties of (1) cohesiveness, indicated by roman numerals, the numbers becoming larger as stickiness diminishes (and malignancy therefore increases), and (2) rate of growth, indicated by letters of the alphabet, "a" for the slowest growing. I presented one such classification,[1] but modification improves it. My present classification combines histologic (cohesion) with clinical (growth rate) judgments and so should possess real prognostic value.

There are other factors essential to accurate prediction, including (1) stage of advancement of the tumor, (2) location and accessibility of the tumor, (3) the presence or absence of metastases and (4) histologic evidence of completeness of surgical removal (i. e. ample margins in three dimensions). An additional factor, not always included in such a list, is the physician who treats the patient. My classification (table 1) conforms to the fundamental reasons for the existence of degrees of malignancy insofar as I understand them.

Table 2 summarizes the data on the tumors presented, comparing my classification with that of Broders as it is used in two Kansas City hospitals. Dr. Ferdinand Helwig, pathologist of St. Luke's Hospital, classed the lesions according to his version of grades I to IV, as judged from the

18. Sutton, R. L., and Sutton, R. L., Jr.: Calcifying Epithelioma, Arch. Dermat. & Syph. **31**:48-57 (Jan.) 1935.

illustrations used here, and Dr. Robert Koritschoner, of Menorah Hospital, classed them comparably but used only grades I to III. There are correlations (1) between the complexion [19] of the patient and the existence of cutaneous epithelioma and (2) between the stage of advancement (quantity) of the tumor and the therapeutic result. Little lesions

TABLE 1.—*Classification of Malignancy of Epidermal Neoplasms*

| Coherence (Histologic Estimation) | Rate of Growth (Clinical Estimation) | | |
|---|---|---|---|
| | A (Slow) | B (Moderate) | C (Fast) |
| I (strong): Progress by spread at dermoepidermal junction as stratified band, which warps and folds | Quiescent warty keratoses<br>Quiescent thick leukoplakias<br>Cutaneous horns<br>Slowly progressive, vegetative, stratified squamous cell epitheliomas containing large pearls with thick epithelial borders<br>Most basal cell epitheliomas | Progressive warty keratoses<br>Progressive thick leukoplakias<br>Vegetative squamous cell epitheliomas with well developed pearls showing stratified epithelial borders<br>Transitional cell epitheliomas with stratified epithelial structure<br>Some basal cell epitheliomas | Rapidly progressive warty keratoses<br>Rapidly progressive thick leukoplakias<br>Vegetative and ulcerative epitheliomas with well developed pearls showing stratified squamous epithelial structure, generally slow to metastasize<br>Some transitional cell epitheliomas<br>Some basal cell epitheliomas |
| II (moderate): Progress by spread at dermoepidermal junction as sheet of single cell thickness, folding, supplanting and engulfing | Quiescent scaly keratoses<br>Quiescent scaly leukoplakias<br>Squamous cell epitheliomas containing pearls with thin epithelial borders | Progressive scaly keratoses<br>Progressive thin leukoplakias<br>Vegetative and/or ulcerative squamous cell epitheliomas containing pearls with thin epithelial borders | Rapidly progressive keratoses with thin scales, bleeding readily<br>Rapidly progressive erythroplakias<br>Ulcerative epitheliomas containing pearls with thin epithelial borders, metastasizing readily |
| III (weak): Progress by intraepithelial, becoming intracutaneous, infiltration of single cells and small groups of cells; cornification of single cells and small groups gives "anaplastic" appearance | Inactive scaly keratoses which bleed readily<br>Inactive flaking leukoplakias and erythroplakias<br>Quiescent intraepidermal Bowen's and Paget's diseases | Progressive keratoses with thin scales, bleeding readily<br>Progressive erythroplakias<br>Early and late lesions of Bowen's and Paget's diseases<br>Ulcerative epitheliomas with cornification of single cells and small groups of cells | Rapidly progressive Bowen's type of keratoses becoming infiltrative epitheliomas<br>Rapidly progressive Bowen's and Paget's diseases<br>Early nodular, infiltrative, intracutaneous, "anaplastic" epitheliomas with central spike<br>Ulcerative infiltrative, epitheliomas with cornification of single cells and small groups of cells, metastasizing readily |

are easy to cure. Table 2 illustrates the differences of opinion that inevitably exist in histologic interpretation. Tumor 1187 (specimen 4), which I believe to be a basal cell lesion, was considered squamous cell by both consulting pathologists. Tumor 829 (specimen 11), which I consider basal cell, was called highly malignant squamous cell by Dr. Helwig. Dr. Koritschoner would give no grade for basal cell lesions, though he agreed with my diagnosis of this tumor. In my scheme, basal

19. Taussig, J., and Williams, G. D.: Skin Color and Skin Cancer, Arch. Path. **30**:721-730 (Sept.) 1940.

TABLE 2.—*Summary of Data on the Tumors Presented.*

| Specimen | Patient: Sex | Patient: Age | Complexion | Fig. | Location | Duration | Stage of Development | Clinical Diagnosis | Growth Rate | Structure | Coherence | Class, Sutton | Grade I to IV, Helwig | Grade I to III, Koritschoner | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ♂ | 87 | Fair | 2 | Ear | 6 mo. | Well developed | Cutaneous horn | Fast | Squamous cell, stratified | Strong | I (c) | Benign | I | Cure, 9 yr. |
| 2 | ♀ | 65 | Fair | 2 | Scalp | 4 yr. | Small recurrence | Basal cell epithelioma | Slow | Squamous cell, stratified | Strong | 1 (a) | I | II | Cure, 2 yr. |
| 3 | ♂ | Old | Fair | 3 | Face | ? | Well developed | Warty squamous cell epithelioma | ? | Transitional cell, stratified | Strong | I (? a) | I | II | Cure, 6 yr. |
| 4 | ♂ | 49 | Fair | 4 | Face | "Several years" | Subepidermal | Keratosis | Slow | ? Basal cell, folded sheet | Moderate | II (a) | Squamous, II | II | ? |
| 5 | ♂ | 47 | Fair | 5 | Face | 2 yr. | Advanced | Ulcerative squamous cell epithelioma | Moderate | Squamous cell, "anaplastic" | Weak | III (b) | II | III | Cure, 8 yr. |
| 6 | ♂ | 75 | Fair | 6 | Ear | 6 mo. | Well developed | Warty squamous cell epithelioma | Fast | Squamous cell, thin bordered pearls | Moderate | II (c) | II | I | Cure, 8 yr. |
| 7 | ♀ | ? 45 | Medium | 7 | Lip | ? | Well developed | Squamous cell epithelioma | ? Moderate | Squamous cell, stratified | Strong | I (? b) | II | I | Cure, 7 yr. |
| 8 | ♂ | 63 | Fair | 8 | Lip | 1 yr. | Advanced | Infiltrative squamous cell epithelioma | Fast | Bowen's disease, advanced | Moderate | II (c) | III | II | Death |
| 9 | ♂ | 69 | Fair | 8 | Nose | 3 mo. | Small | Squamous cell epithelioma | Fast | Bowen's disease, early | Moderate | II (c) | III | III | Cure, 1 yr. |
| 10 | ♂ | 42 | Fair | 8 | Lip | 3 yr. after first operation | Advanced recurrence | Infiltrative squamous cell epithelioma | Fast | Bowen's disease, advanced | Weak | III (c) | III | III | Death |
| 11 | ♂ | 78 | Fair | 9 | Face | "3 or 4 yr." | Shallow | Early epithelioma | Slow | Basal cell, stratified | Strong | I (a) | Squamous, III | Basal, no grade | Cure, 5 yr. |

cell and squamous cell lesions are both classified. The table shows that broadly, although not in every detail, the judgments of all three observers were similar.

The estimation of malignancy is a complex intellectual business, and it rests on more than histologic data alone.

Agreeing to the criticism that there is a considerable subjective element in any classification, I insist that other classifications are no less subjective, no more informative and to no greater extent based on plausible theories than mine.

The cohesiveness of epithelial cells is dependent in part at least on the degree of vascularity in Montgomery's opinion [20]; but the vascularity is dependent in part at least on the degree of cohesiveness in my opinion, for loose cancer cells provoke more inflammation. Montgomery pointed out that a venereal wart or a lesion of Darier's disease may show little coherence of the cells and a rapid rate of growth; but in my opinion these cells are normal ones that are sick and not neoplastic cells at all and so are not pertinent to the discussion.

Montgomery [20] agreed that "The benign or malignant character of a solitary lesion or the degree of malignant change that may develop in the future cannot be accurately predicted either clinically or pathologically." Yet he had the temerity to apply statistics concerned with the future behavior of many lesions collectively, when of each one of them individually he admitted ignorance. His trouble lay in interpreting "senile keratoses;" these lesions are—all of them I say—epidermal neoplasms, analogous to the keratoses provoked by carcinogenic chemicals. Each is an individual neoplasm. Statistics regarding them are empty. Montgomery [20] wrote:

> I do not believe that Bowen's disease ever eventuates in basal cell epithelioma. From the beginning, pathologically, it is squamous cell epithelioma. . . .
>
> Bowen's disease was first described by Bowen, correctly, I believe, as a precancerous dermatosis.

If things equal to the same thing are equal to each other, my reasoned conviction [1] that the word "precancerosis" lacks meaning is not weakened by his argument.

Montgomery [20] accredited the importance of considering the patient and his susceptibility (e. g. complexion [19]) to the unknown etiologic factors, "rather than basing analysis on individual lesions." I prefer to analyze individual lesions, finding them problematic enough, for "lesions" taken collectively offer still greater difficulties. There is only one way to arrive at dependable statistical knowledge of a person's keratoses, and that is to identify them one at a time as they appear and

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20. Montgomery, H.: Precancerous Dermatosis and Epithelioma in Situ, Arch. Dermat. & Syph. **39**:387-408 (March) 1939.

to follow each throughout the remainder of that patient's life, subjecting each to histologic study after necropsy. If this were done, not in a single case but in many, the incidence of malignant growths might be determined; and it might be 20 per cent, but the fact would not be very important. One knows already that a keratosis should be destroyed, for some "keratoses" are early carcinomas, while all keratoses (of the kind under discussion) are epidermal neoplasms. Such keratoses develop when chemical carcinogens are applied to the skin, and some of them progress while others do not. For instance, when Mider and Morton [21] applied methylcholanthrene a single time to 44 C57 brown mice, in 16 animals twenty-two papillomas developed, first appearing from twenty-six to sixty days after the application; of these papillomas, fifteen regressed completely and seven remained, and of the seven, three proved to be malignant. In this experiment, 13.6 per cent of the keratoses were epitheliomas. Edens [22] expressed, I think, the correct clinician's view that all keratoses should be considered "potentially malignant."

Montgomery [20] made the following statement:

> I have studied specimens from several hundred lesions of precancerous dermatoses of different types, especially in the earliest stages including more than 100 specimens of senile keratoses, in which the incidence of epithelioma remained at 20 to 25 per cent, in contrast with an incidence of less than 2 per cent in most types of benign dermatoses.

How did he get the statistic "20 to 25 per cent?" If his file, which was labeled "senile keratoses" and contained one hundred specimens, contained in truth twenty epitheliomas according to his own statement, why did he not correct his file until it contained only "senile keratoses" and relabel the "epitheliomas" as such? Montgomery recognized in my illustrations [1] "evidence of frank malignant change easily diagnosed." True, but clinically the doubt was real in some of the cases. Would one diagnose specimens 4 or 11 of this article clinically as epithelioma rather than "precancerosis?" I should, but some authors disagree with me. What is illustrated in *VII* of figure 9 clinically, a keratosis or an epithelioma?

Montgomery [20] "cannot see the value of classifying epidermal neoplasms on the basis of coherence of the cells rather than by the generally accepted method of classification and grading employed by Broders." I reply that I see no vital compulsion for classification of any kind:

> Persons unfamiliar with the minute structure of the diseases they meet have no business treating them, neoplasia of the mouth, especially, where error is

21. Mider, G. B., and Morton, J. J.: Skin Tumors Following a Single Application of Methylcholanthrene in C57 Brown Mice, Am. J. Path. **15**:299-302 (May) 1939.

22. Edens, L. E.: Cutaneous Precancerosis, Texas State J. Med. **36**:29-33 (May) 1940.

disastrous; and this statement is intended specifically to apply to those who wish their microscopy to be supplied for them secondhand in the sugar coated form of "grades." [23]

"General acceptance" is not proof of validity. It is readily possible to design a valid logical structure in which false premises imply correct conclusions.[24] An example may be presented as follows: With an American penny in the hand, one argues, "All brown coins are made of copper. This is a brown coin. Therefore it is made of copper." While the argument is sound logic, its first premise is not admissible. Analogously Broders has in effect argued, "Malignancy depends on differentiation: the less the differentiation, the greater the malignancy. This tumor is undifferentiated. Therefore it is highly malignant." I take issue with his premise regarding differentiation, for I interpret the structure of a tumor in terms of cohesiveness of the cells and their rate of growth. If the cells are not cohesive, a demonstrable physical property, and if they grow rapidly, a demonstrable clinical phenomenon, then the visible histologic result is what Broders would call "undifferentiation." Such a tumor would be judged malignant by both of us, but, I believe, by him for wrong reasons. I argue in favor of my premise, which I think is sound and material while his appears to me to be a hypothetic abstraction filled with subjectivity.

### MANNER OF ORIGINATION OF EPITHELIOMA; "PROGRESSIVE CANCERIZATION"?

Brunschwig and Tschetter [10] made the following assertions:

> Microscopic study of small and early squamous cell carcinomas and of the so-called precancerous lesions . . . reveals that the processes involve a segment of the epithelium and that they are not the result of changes arising in one cell or a small nidus of cells. At the margins of such lesions are zones of direct continuity [intergradient transition] between normal and abnormal epithelium, and in such zones it is not possible by present staining methods to distinguish which cells are normal and which are neoplastic.

These authors' study concerned especially the lesions induced in from sixty to ninety days on the backs of white mice by triweekly applications of 0.3 per cent methylcholanthrene solution in benzene. In support of this conclusion they presented fourteen photomicrographs, of which interpretation can indeed be different from their own. Their figure 1 purports to show "initial" changes occurring over a segment of epithelium. In this figure I see a wide cutaneous area covered by abnormal

23. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1473.

24. Richardson M.: Fundamentals of Mathematics, New York, The Macmillan Company, 1941, p. 10.

epidermis of strong coherence. Corneum derived from this is likewise different from normal and is strongly coherent. The lesion required at least sixty days to reach its present condition, yet they considered it an initial change. They denoted zones of "direct continuity with normal epithelium at margins of lesion where accurate differentiation of cells of lesion and normal cells can not be made." Yet at the left, just medial to *Z*, the distinctive break where normal and abnormal corneums are in juxtaposition is plainly visible even at this low magnification and is analagous to the break seen in my figure 2 (*V*). In their figure 2 they show "downgrowth of epithelial cell masses (like stalactite) from superficial layer of epithelium—further histologic evidence of segmental origin of such lesions." They presumed that the epidermis here was normal and that the tumor came from it. This is not so; the epidermis was tumor tissue too [8]; compare with my figures 3 (*IV*), 6 (*VI*) and 7 (*V*). In their figure 2 the pallor of tumor tissue contrasts with the darkness of hypertrophic normal at the right, and the conjunction zone, deserving study at higher magnification, is nevertheless discernible in their picture. In their figure 3 the epithelium which bears the label normal looks to be not normal but part of the tumor, for the picture, showing an inadequate amount of surface, is of no use to one who has not examined the section from which it was photographed. In their figure 4 the frayed end of normal epidermis is disrupted and undermined by tumor cells, just as in my figures 5 (*II*) and 6 (*VI*), and they recognized this as a "distinct break." In their figure 5 normal epithelium was fused with the stratified tumor epithelium, and their zone (*Z*) denoted where "malignant and non-malignant cells are not distinguished." They could be distinguished, I am sure, by higher magnification, for this is a junction similar to that in my figure 8 (*XI*). Their figure 6 shows a junction also resembling that in my figure 8 (*XI*). At the frayed termination of the epidermis they noted "where cells from the edge of the receding normal epithelium appear to be undergoing carcinomatous degeneration and, *streaming downward into the lesion* [italics mine], appear to contribute to it." This phenomenon, veritably a cellular waterfall and not a mere stream if it existed, would be an astonishing thing, a hive of cellular activity. What they and I look at is the same, but what we see is different: I see fusion of a few cancer cells with a few normal cells at their point (*CX*), as in my figures 5 (*II*) and 6 (*VI*). Their figure 7 shows "infiltration of squamous epithelium of skin by cords of breast carcinoma cells. . . . Such a picture is not seen in normal epithelium about squamous cell carcinomas of the skin." Compare with my figures 6 (*IV*) and 8 (*VIII*). Such a type of lateral spread does not occur in squamous cell epithelioma, I partly agree with them, for when it does occur the lesion is given the diagnosis Bowen's disease or Paget's disease. Bowen's disease is a kind of squamous cell epithelioma,[20] as seen in my figure 8 (*II*).

Intimate study of the whole article of these authors reveals the same kind of objectionable interpretations.

The manner of lateral progress is seen from my illustrations to consist of tumor cell proliferation which undermines, supplants, engulfs and replaces normal epithelium, spreading at the dermoepidermal junction. "Progressive cancerization" at the edges of a cancer is in truth a phenomenon of replacement of normal by abnormal cells. It is not a phenomenon of alteration of normal cells into cancer cells.

When Brunschwig and Tschetter [10] encircled small lesions by tattooing dots into the dermis at their edges, the tumors grew in diameter without concomitant increase in diameter of the circle of dots. Thus epithelial changes occurred without displacement of fixed mesodermal tissues, although epithelial tissue overlying a tattoo mark thickened so as to obscure the dot from visibility. This interesting experiment shows only that fibrous tissue does not move about even when considerable dislocation of overlying epithelium takes place. It demonstrates nothing else concerning the nature of enlargement of the epithelial disease.

Tumor cells grow where they can grow. A cancer behaves as if it were a colony of cells like one another but different from normal ones. When Brunschwig and Tschetter [10] decided that there occurs "progressive cancerization of normal epithelium in the immediate periphery of certain squamous cell carcinomas as a factor (in addition to centrifugal expansion of the lesion because of multiplication of its cells) in the continued lateral spread of such lesions," I judge their conclusion to be erroneous.

### OTHER EXAMPLES OF JUNCTIONS OF NORMAL WITH CANCEROUS EPITHELIUM

Junctions of normal with cancerous epithelium are seen in numerous published illustrations, of which I have selected a few for discussion. Vickers, Jackman and McDonald,[25] reporting cases of early carcinoma of the anus, showed in their figure 2 "abrupt transition from benign to carcinomatous epidermis with intact basement membrane." They agreed with Broders that epithelioma in situ is a "condition in which malignant epithelial cells have not migrated beyond the juncture of epithelium with connective tissue, the so-called basement membrane."

In the treatise of MacKee and Cipollaro [26] figure 31 (page 33) shows epithelioma in situ, with replacement of epidermis by tumor cells near the follicle orifice at the top and early undermining at the right; tumor

25. Vickers, P. M.; Jackman, R. J., and McDonald, J. R.: Anal Carcinoma in Situ: Report of Three Cases, South. Surgeon **8**:503-507 (Dec.) 1939.

26. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, American Journal of Cancer, 1937.

cells and normal cells are distinct. Their figure 29 (page 31) shows a junction found by following from the left the basal epidermal layer to the right side of the fourth dermal peg; corneum derived from cancer cells is parakeratotic. Their figure 36 (page 37) shows subepidermal spread of early cancer, with beginning engulfment of the sebaceous follicle from above, along the dermoepidermal junction. Their figure 37 (page 38) shows a firmly fused conjunction in which tumor cells, evidently strongly coherent, are yet clearly paler than normal ones. Their figure 41 (page 41) shows strands of cancer cells "extending from the under surface of thinned epidermis"; here the surface is cancerous [8] (compare with *V* in my figure 7). Their figure 152 (page 129) shows a stratified transitional cell tumor much like *III* in my figure 3. I should not have written their title "from a somewhat thickened epidermis there extends down into the derma an irregular mass," etc., for I should say juxtaposition is evident. In their figure 194 (page 159) the circumscription of Paget cells from surrounding normal cells is well illustrated. They titled their figure 200 (page 163) "Hyperplastic epidermis covered by closely laminated horny layer. The hyperplasia of the epidermis," etc. I insist that here one sees epidermis composed wholly of tumor cells (compare with *IV* in my figure 3). In their figure 202 (page 165) the transition from hypertrophic normal to Bowen's type of cancerous epidermal replacement is seen to the left of the fifth dermal papilla from the right margin of the cut.

In Eller's book [27] figure 125 (page 192) shows a single layer sheet of cancer cells at the dermoepidermal junction, titled "senile keratosis with beginning carcinoma." Compare with *VI* in my figure 5 (also see Sutton and Sutton [28]). His figure 160 (page 228) shows the sharp edge of a squamous cell carcinoma at the right margin, and so does his figure 168 (page 236). His figure 149 (page 216) shows in a roentgen ray keratosis tumor epithelium only, except at the upper right, where corneum of normal cell derivation is seen. His figure 196 (page 269) is a particularly good illustration of pseudoepitheliomatous hyperplasia.[12] He depicted in figure 217 (page 289) an interesting intraepidermal basal cell carcinoma; much of the normal epithelium here shows pseudoepitheliomatous hypertrophy.

Examples of abrupt transition of cell type in early squamous epithelioma of the cervix uteri are seen in figures 14 and 15 of Meyer's paper,[28a] and this author adjudged his lesions by no means precancerous.

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27. Eller, J. J.: Tumors of the Skin, Benign and Malignant, Philadelphia, Lea & Febiger, 1939.

28. Sutton and Sutton,[11] p. 388.

28a. Meyer, R.: The Histological Diagnosis of Early Cervical Carcinoma, Surg., Gynec. & Obst. **73**:129-139 (Aug.) 1941.

### HISTOLOGIC EVIDENCE OF INCEPTION; MUTATION AND INDUCTION

The inception of an epithelioma must be traced backward in time to a commencement antedating such lesions as shown in figure 1 of Brunschwig and Tschetter [10] and in figure 1 of my earlier article.[1] To attempt this histologically entails risk of making unwarranted inferences. In figure 5 *I* of the present article the epidermis is all epithelioma from *a* to *b*; to a distance on both sides of the central region extension of the epithelioma is subepidermal, and it attains definite terminal points. If one imagines this lesion to regress in time, one visualizes tumor tissue receding from the terminal points, and one puts back normal epidermis, now exfoliated. The tumor tissue must have arisen, I think, from a nidus located somewhere about *b*, where the cancer is seen now to have reached its greatest development.

Time intervals and movement can be inferred from a histologic preparation, although duration and motion cannot be seen. As I [1] have shown, it requires about a week for normal epidermis to replace itself by proliferation of basal cells. One of each pair of daughter cells is located externally, and further proliferation eventuates in externalizing cells of the stratum mucosum until they are finally cornified and shed. Their cornification is a degenerative, necrobiotic phenomenon,[2] I believe, and not "differentiation." The normal direction of externalizing movement is approximately perpendicular to the epidermal surface. In figure 1 the junctions are more or less perpendicular, representing the approximately equal rates of growth of the chick and human epithelium. In *IV*, *V* and *VI* of figure 3 histologic evidence of progress seems unimpeachable. In *VI* of figure 3 the upper extent of living normal epidermal cells was at *a* and is at *b*.

Do these lesions originally arise from single mutant cells or from a number of cells? The answer must be hypothetic. One sees in each case that all the tumor cells look like members of the same family, and it is easier to imagine that they derived from one cell than from many, "for the probability is slight that several cells should alter in the same way and give rise to progeny which are indistinguishable." [1]

There is always a prolonged period of some thirty to one hundred days between the application of a carcinogen and the appearance of visible tumors. I [1] "believe the inability to observe lesions before one hundred days had elapsed [referring to Mottram's experiments [13] with tarring mice] is to be explained by the fact that until the epidermis was entirely replaced by the progeny of the altered cell no visible lesion would exist, and such replacement requires time." In figure 5 is demonstrated the subepidermal spread in continuity, where gross tumor is

observed only in *I* from *a* to *b*; but this carcinoma extends far external to *a* without giving any clinical cue to its presence in *VI, VII* and *VIII*. It is entirely possible for small quantities of a carcinoma to exist and proliferate beneath the epidermis unaccompanied by a lesion visible to the unaided eye.

Pullinger [29] studied the immediate results during the first four days after the application of methylcholanthrene and other carcinogenic agents to the skins of mice. A single treatment with rapidly acting carcinogenic chemicals caused severe damage to epithelium and acute inflammation of subepidermal tissue. A striking feature of the reaction was the degree of injury from which the cells recovered. Progressive swelling of cells, nuclei and nucleoli with cytoplasmic degenerations were seen together with evidence of differentiation. The reaction was generalized over the whole of the treated area, and the margin was rather sharply defined. Squamous epithelial cells and nuclei swelled, he reported; the cytoplasm became vacuolated, and multiplication, at first by direct and later by indirect division, followed. The increase in size of cells and nuclei was progressive, and further cytoplasmic degenerations appeared in some of the cells while others showed signs of recovery. While noncarcinogenic hydrocarbons and other chemicals were tested, none, Pullinger determined, evoked reactions such as apparently specifically follow the application of active carcinogens. In view of this study, I am prepared to believe that cancerous mutation is induced in normal cells by carcinogens in a short time. The clinically visible result of the alteration requires time to develop.

Keratoses and epitheliomas "comprise a series of new growths composed of keratinizing epithelium which are identical with the lesions of xeroderma pigmentosum and with the lesions provoked by carcinogenic substances such as tar or dibenzanthracene, or by radiodermatitis . . . [Sutton and Sutton [28]] group the lot as epidermal neoplasms." Rous and Kidd [30] studied the problem of whether tar warts on the skins of rabbits are tumors and decided that they are, being

> benign growths expressive of slight yet irreversible deviations of epidermal cells from the normal. . . . Often the neoplastic cells resume the normal aspect and habit of life long before the tumor mass is gone; and they may persist as part of an apparently normal epidermis, retaining their neoplastic potentialities for months after all signs of the growth have disappeared. . . .
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> It is plain that the neoplastic state does not necessarily connote independence of behavior or success in tumor formation.

29. Pullinger, B. D.: The First Effects on Mouse Skin of Some Polycyclic Hydrocarbons, J. Path. & Bact. **50**:463-471 (May) 1940.

30. Rous, P., and Kidd, J. G.: Conditional Neoplasms and Subthreshold Neoplastic States: A Study of the Tar Tumors of Rabbits, J. Exper. Med. **73**:365-390 (March) 1941.

MacKenzie and Rous [31] continued this study by tarring rabbits' ears, punching a hole in an ear at the edge of a wart and observing the manner of repair. The regenerating epithelium that covered the defect was derived in part from normal and in part from altered epithelium. They decided that "A carcinogenic tar . . . renders many more epidermal cells neoplastic than ever declare themselves by forming tumors." The altered cells were originally not different from other normal ones. Altered, they apparently lay latent for long periods and eventually responded to noncarcinogenic stimulation by multiplying into growths. These observations are in agreement with judgments I have often expressed regarding the neoplastic nature of spontaneous human keratoses.

With regard to the theory of origin in somatic mutation, Rous and Kidd [30] argued:

> The view . . . rests on an analogy which breaks down when the attested mutations of this sort are scrutinized. . . . For all of the mutated cells which have thus far come to attention continue to obey the general laws of organization, and . . . do not form tumors. . . . Corolla dots, delphinium flowers, fern pinna, and skin patch [examples of recognized somatic mutation] they all remain, none constituting a tumor. In mammals somatic mutations are exceedingly rare.

In so arguing, they are on dubious ground, like the man who on first seeing a giraffe said, "There isn't any such animal." Corolla dots and other phenomena which they accepted as somatic mutations represent mutation of somatic cells comparatively early in the embryologic development of the soma. On the other hand, keratoses, which are, I insist, plausibly interpreted as the result of somatic mutations, represent mutation of epithelial cells late in the embryologic development of the soma as a whole. The rarity of mammalian somatic mutations may be due to failure to recognize that which is commonly before the eyes. The epidermis, continually proliferating, is an "embryonic" tissue throughout life.

Spemann's organizers and induction whereby ectoderm is impelled to form structures which it would not form in normal development were discussed by Foulds [3]:

> Organizers exert an induction action only on tissues which are in a receptive state known as "competence." Inductions start the process of determination whereby the fate of a region is decided and its competence lost; the tissue is then "self-differentiating."

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31. MacKenzie, I., and Rous, P.: The Experimental Disclosure of Latent Neoplastic Changes in Tarred Skin, J. Exper. Med. **73**:391-416 (March) 1941.

Two kinds of induction are recognized: (1) evocation, which starts the process of differentiation but does not direct it qualitatively, and (2) individuation, which directs the course of differentiation qualitatively and is caused apparently only by living cells. Carcinogenic hydrocarbons can produce squamous cell carcinoma, Foulds stated, from any epithelium having the inherent capacity for squamous cell differentiation, including kidney, prostate and breast. "Organizers evoke normal organization even in unusual locations," as I [1] have said, "while the result of carcinogenesis is disorganizing."

The inductor is a chemical substance allied to the ether-soluble sterols, according to Leslie-Roberts.[32] Its activity does not depend on nucleus, cytoplasm or life of cells or organs. Its sole requirement is the living cell structure of the host. Present in all parts of an embryo, it operates on ectoderm from the mesoderm. Therefore, Leslie-Roberts felt, the center of interest passes from histology to chemistry. But histology is not barren, I think. Foulds [3] stated the following belief:

> It is improbable that the study of tumor structure alone will yield dramatic results. . . . Yet histology is still indispensable in the interpretation of many experimental results; it has provided the basis for all modern investigations of cancer, and it has disclosed an important fraction of the facts which a satisfactory theory of cancer must embrace.

I do not know how to choose between the mutation and induction hypotheses of tumor origination. Once originated, however, an epithelioma of the skin behaves as if it were a colony of one kind of cells, different from normal ones. Insofar as my histologic studies reveal the nature of growth and spread of cancer, this is so, and I am certain that "progressive cancerization" of normal cells into tumor cells, in the Brunschwig-Tschetter connotation, is an untenable hypothesis.

## MULTICENTRIC ORIGIN

"Situation next" does not prove "derivation from," though according to Montgomery's experience [20] "with both basal cell epithelioma and squamous cell epithelioma in situ, one is more likely to see evidence of multicentric points of origin in the epidermis than evidence of epithelioma developing from a solitary cell." One is likely to see, I say, what one wishes to see—the puzzle is not what one sees but what is there. In "superficial multicentric basal cell epithelioma" one sees clinically a solitary lesion which gradually expands in diameter, while microscopically one sees (in the usual, single, perpendicular sections) isolated masses of tumor tissue in juxtaposition with the epidermis at its under

32. Leslie-Roberts, H.: The Growth of Epithelium in Tegumentary Tissues, Brit. J. Dermat. **51**:405-417 (Oct.); 451-468 (Nov.) 1939.

surface. But if the lesions are sectioned parallel with the surface and serial sections are made, as Madsen [33] studied them, one learns according to Madsen:

> This carcinoma has a central place of origin, from which it grows continually in radial (peripherad) direction along the interpapillary processes or ridges in the epithelium. The tumor degenerates in pieces centrally, thus leaving isolated isles of carcinoma (of which a few only are connected with a hair follicle), while the tumor tissue in the peripheral region of the patch forms practically speaking a continuous belt.

Similar facts are true of the Bowen type of superficial squamous epithelioma (see my specimens 8 and 9, fig. 8, *I* to *IX*), according to Madsen.

On examination, Madsen's arguments carry conviction. The same kind of subepidermal spread of cancer is indicated in my figures 3, 4, 5 and 9, the cell type in 5 being squamous, in 4 and 9 basal and in 3 intermediary.

### FORMS OF EPITHELIOMA

There is only one form of cutaneous epithelioma, MacCormac [34] suggested, rather than two main forms (basal cell and squamous cell). The predominating cell type is an expression, he submitted, "of the rate of growth rather than an indication of the layer of the epidermis from which the tumor originates." I prefer to suppose that there are many cell races in cutaneous epitheliomas, each representing one of the many cell types which are possible derivatives from normal epithelium, by mutation, induction, virus or whatever does institute the change, and that each tumor is an individual thing with properties of its own differing from the properties of normal tissues which it may resemble in appearance. This view dissolves Pinkus' dilemma [35] as to why the cells of malignant squamous lesions resemble the less active layers of the epidermis while those of comparatively benign basal cell lesions resemble the normally more active layer. In a new kind of cell resemblance tells little of the rate of growth, on which to a large extent depends the malignancy of the homogeneous colony which is the epithelioma. Of the many kinds of individual epitheliomas which fall within the alternative potentialities

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33. Madsen, A.: Du mode de croissance de l'épithéliome basocellulaire superficiel, Acta dermat.-venereol. **21**:514-523 (May) 1940; The Neoplastic Nature of Bowen's Disease: Examination of a Flat Lesion in Horizontal Sections, ibid. **22**:24-34 (Feb.) 1941; abstracted in Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, 1941, p. 494.

34. MacCormac, H.: Cancer of the Skin, Brit. J. Dermat. **52**:141-155 (May) 1940.

35. Pinkus, H.: Some Uncommon Skin Tumors, J. Michigan M. Soc. **37**:533-537 (June) 1938.

of epithelial life, some are common and others rare, and groups show family resemblances, as separate mutants may resemble one another.

Four basic structural forms of clinical early epithelioma of the skin can be distinguished:

(1) *Subepidermal spread in stratified sheets of more than single cell thickness,* which replace normal epidermis and warp and fold to form warty keratoses and pearl-containing downbuddings and insinuate themselves along the dermoepidermal junction so as to undermine, supplant and engulf epidermis and accessory structures. This form represents strong cohesion, and clinical examples are warty keratoses, leukoplakias and usually vegetative epitheliomas of relatively low malignancy, as seen in figures 2, 3, 7 and 9 (table 1, I A, B and C).

(2) *Subepidermal spread in sheets of single cell thickness,* which fold to form the earliest downbuddings and insinuate themselves along the dermoepidermal junction (line of least resistance), so as to undermine, supplant and engulf epidermis and accessory structures. This form represents moderate cohesion, and clinical examples are scaling keratoses, erythroplakias and ulcerative epitheliomas of considerable malignancy, as seen in figures 4, 5 and 6 (table 1, II A, B and C).

(3) *Subepidermal spread in single cells and small groups of cells.* This form represents weak cohesion and appears clinically first as a minute intracutaneous nodule, from the center of which may extend a tiny horny spike. Within, noncohesive growth is speedy, "anaplastic," invasive and highly malignant, as in figure 6 of my earlier article,[1] while necrobiotic cornification of single cells and small groups of cells generally occurs (table 1, III A, B and C).

(4) *Intraepithelial spread in single cells and small groups of cells.* This, like the third form, represents weak cohesion and appears clinically as Bowen's disease or Paget's disease, which are varieties of keratinizing epithelioma, usually of rapid growth rate, as seen in figure 8.

## RECURRENCE

Subepidermal extension of the epithelioma beyond the boundary of the grossly detectable tumor accounts for many therapeutic failures and recurrences. What a surprisingly wide margin must be sacrificed in tumor 143 (fig. 5) in order to cure this lesion by surgical intervention! Keratosis surrounding an intramesodermal squamous cell epithelioma is an epidermal portion of it. Leukoplakia surrounding a mucosal epithelioma is an epidermal part of it. Neoplastic leukoplakias, like senile keratoses, are sharply marginated,[11] and they must be destroyed when the main tumor mass is destroyed if permanent cure is to be obtained, for failure to destroy them is failure to eradicate the whole of the tumor.

## COMMENT

The mutation hypothesis is a satisfying one, Auerbach [36] believed, for it "seems to offer the most plausible explanation for the phenomena of cancer, and to be the one which requires the least in the way of additional hypotheses." Auerbach's studies concerned gene mutation provoked by ultraviolet radiation in Drosophila, in which she obtained maximum effect at 265 millimicrons corresponding to the maximum absorption of nucleic acid, a chromosome constituent, while this wavelength is not the absorption maximum for proteins and other cell constituents. Pertinently, Cysticercus fasciolaris, larva of Taenia taeniaformis (the cat tapeworm), often provokes malignant sarcoma in rats, and the greater the number of cysts the more likely is one to be a provocator of sarcoma, according to Curtis, Dunning and Bullock.[37] The age of the rat is less significant than the duration of infestation; so evidently chance plays a part in causation. When sarcoma develops in an infested rat, the lesion begins in only a small area of only one of many cysts. The author stated the belief that this evidence supports the mutation hypothesis.

There is no histologic evidence of which I am aware—nor perhaps can there be—showing the derivation of cancer cells from normal ones, unless, in such a study as that of Pullinger,[29] the immediate alteration of normal cells by chemical carcinogens represents this phenomenon. Once altered, the change is irreversible.[38]

## SUMMARY

1. Whole tumor sections of small and early, as well as advanced, epitheliomas of the skin are presented so as to illustrate the manner of spread of cancerous epithelium.

2. Fusions of chick with human epithelium, in Goodpasture's grafts of human skin onto chorioallantois of chick embryos, demonstrate what fusions between two kinds of epithelium look like. Comparable fusions join cancerous and normal epithelium in spontaneous human tumors.

3. "Progressive cancerization" at the edges of cutaneous epitheliomas is judged a misinterpretation of histologic data, which reveal abnormal cells only in juxtaposition to normal ones, undermining, replacing and engulfing them. No evidence of conversion of normal cells into cancerous cells is found in diagnosable epitheliomas of the human skin.

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36. Auerbach, C.: Tests of Carcinogenic Substances in Relation to the Production of Mutations in Drosophila Melanogaster, Proc. Roy. Soc. Edinburgh **60** (pt. 2):164-173, 1940

37. Curtis, M. R.; Dunning, W. F., and Bullock, F. D.: Is Malignancy Due to a Process Analogous to Somatic Mutation? Science **77**:175-176 (Feb. 10) 1933.

38. Gye, W. E.: The Imperial Cancer Research Fund, Thirty-Fourth Annual Report, Brit. M. J. **2**:1276-1277 (Dec. 19) 1936.

4. Malignancy and invasiveness are presented as phenomena intimately concerned with cohesion of cancer cells and their rate of growth. Classification of degrees of malignancy is undertaken on the basis of degrees of cohesion, estimated histologically, in conjunction with rates of growth, judged from clinical observation.

5. A histologic explanation of recurrence is given in the description of specimen 5 (fig. 5).

6. "Precancerosis" is depreciated and its absence of biologic meaning emphasized; attack is made on the validity of the mathematical method used in a statistical attempt to justify the word.

7. In demonstrating the manner of the local spread of eleven epitheliomas of the skin, I have presented evidence which supports the view that clinically and histologically each spontaneous epithelioma of the human skin behaves like a colony of cells of a new kind. Perhaps the new kind comprises the homogenous progeny of one mutant cell.

1102 Grand Avenue.

# TINEA CAPITIS WITH INFECTION OF THE EYELASHES

## REPORT OF A CASE

ROYAL M. MONTGOMERY, M.D.
AND
ESTHER A. WALZER, B.S.
NEW YORK

Few cases of tinea ciliorum have been reported in the literature. Sequeira [1] wrote: "Tinea of the eyelashes is exceedingly rare. I have not met with a case." Sabouraud reported that it is rare in France and less rare in Italy. Weidman [2] also stated that the eyelid is not a common region to be affected by ringworm.

Arijewitsch,[3] Davidson and Gregory,[4] Coutela and Offret,[5] McCarthy [6] and others [7] have reported cases of fungous infection of the eyelashes. In the case reported by Davidson and Gregory Trichophyton album was isolated. In Arijewitsch's case Microsporum lanosum was found. In the case of Coutela and Offret Trichophyton asteroides was the responsible organism. In McCarthy's case Trichophyton granulosum was the cause.

Of 560 cases of tinea capitis (with organisms found on culture) at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital between January 1935 and July 1941—a period of six and one-half years—the case reported here was the only one in

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From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. Sequeira, J. H.: Diseases of the Skin, New York, The Macmillan Company, 1927, p. 182.

2. Weidman, F. W., in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 10, p. 133.

3. Arijewitsch, A.: Zur Frage der Pilzerkrankungen der Augenlider und Wimpern, Dermat. Wchnschr. **90**:683-685, 1930.

4. Davidson, A. M., and Gregory, P. H.: A Case of Kerion Celsi Associated with Ringworm of the Eyelashes Accompanied by a Trichophytid, Canad. M. A. J. **27**:485-487, 1932.

5. Coutela, M., and Offret, G.: Un cas de teigne cilio-palpébrale, Bull. Soc. d'opht. de Paris, 1936, pp. 402-405.

6. McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, p. 365.

7. Cited by Arijewitsch.[3]

Fig. 1.—The central portion of the left upper eyelid is infected with M. audouini.

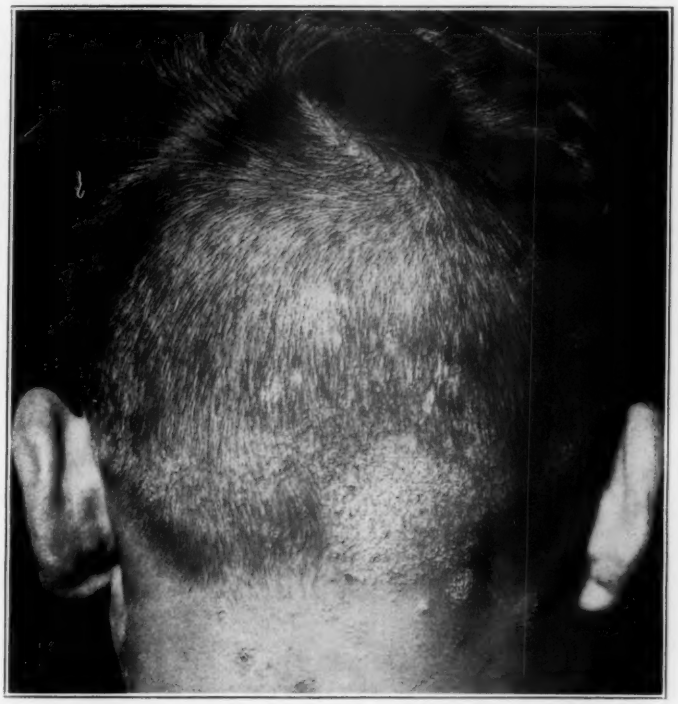

Fig. 2.—Scaly, noninflammatory areas of alopecia caused by M. audouini.

which eyelashes were found to be infected. This unusual location of infection was discovered by examination with filtered ultraviolet rays and not by gross examination. The infecting organism was found to be Microsporum audouini.

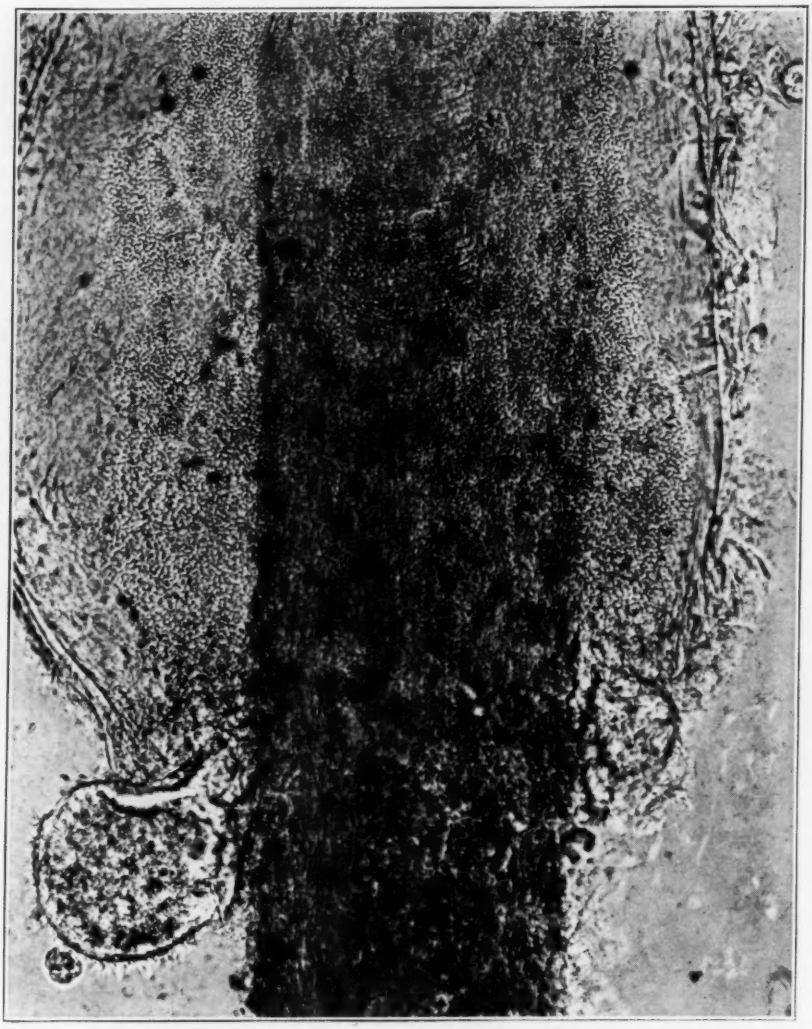

Fig. 3.—Photomicrograph of an infected eyelash, showing the mosaic sheath about the shaft.

REPORT OF CASE

E. L., a boy 11 years of age, was brought to the clinic on April 26, 1941. At that time the eruption had been present for six weeks.

A slightly erythematous scaly area the size of a silver dollar was present in the occipital region. Many hairs were broken off. Surrounding this area were

similar smaller areas with hairs broken off at the base. There was one small patch in the left frontal region where the hair was parted. Scaling was absent on the eyelids. The eyelashes were apparently normal on gross examination.

On examination with filtered ultraviolet rays the hairs in the larger affected area, in many of the smaller surrounding patches and in the left frontal region were observed to fluoresce. Twelve or fifteen hairs on the upper portion of the left upper eyelid fluoresced a typical bright light green.

Hairs from the occipital area and the left eyelid showed many small spores surrounding the shaft. M. audouini was grown from the hair from both locations on Sabouraud's medium.

On May 13 an epilating dose of roentgen rays was applied to the scalp. Some of the eyelashes were epilated manually, and yellow mercuric oxide ointment U. S. P. was prescribed for the eyelids. On June 16 the scalp was devoid of hair, and the eyelash infection had diminished. Only two positive fluorescing hairs remained. There was a large pustule on the margin of the left upper eyelid, and a few pustules and some adenopathy were present on the posterior region of the scalp. On July 1 the eyelid and the scalp were apparently normal and some new hairs had regrown. On August 26 the scalp and eyelid were free from infection and there was a good growth of hair.

The patient's twin brother, who also visited the clinic on July 1, presented a typical circinate patch on the right shoulder, which subsequently proved to be caused by M. audouini.

## COMMENT

This case of tinea capitis illustrates the necessity of examination of the eyebrows and eyelashes, as well as the scalp, with filtered ultraviolet rays to determine the extent of infection.

The involvement of the eyelashes in this case would have passed unnoticed if it had not been for this special examination.

57 West Fifty-Seventh Street.

301 East Nineteenth Street.

# BACTERIOSTATIC EFFECT OF SULFATHIAZOLE IN VARIOUS OINTMENT BASES

ERNEST A. STRAKOSCH, M.D.
AND
VALERIE M. OLSEN, M.T.
MINNEAPOLIS

The management of streptococcic and staphylococcic infections of the skin presents an important problem in daily practice. Of all the pyogenic infections of the skin, impetigo contagiosa is the most common. For this reason and because impetigo is the most superficial type of pyoderma, it offers an excellent opportunity to test treatment by topical applications of bacteriostatic and bactericidal drugs.

It is now established, by the excellent work of Dohi and Dohi,[1] Lewandowsky,[2] Tachau [3] and, more recently, Epstein,[4] that impetigo contagiosa can be of streptococcic, staphylococcic or mixed bacterial origin.

The common treatment of pyogenic infections of the skin has been the use of ammoniated mercury, mercurial lotions, silver nitrate solution or dyes. Although the results with these remedies were generally good, the time which they required to cure ordinary impetigo was rather long, often ten to sixteen days. It was for this reason that we became interested in the local use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfanilamide (paraaminobenzenesulfonamide), hoping to find in them a more specific chemical, which would shorten the time of treatment and also offer a more acceptable form of application.

Since Domagk's report in 1935,[5] the literature has been replete with reports on the administration of sulfanilamide. Subsequent to the

From the Division of Dermatology and Syphilology, University of Minnesota, H. E. Michelson, M.D., Director, and the Department of Dermatology and Syphilology, Minneapolis General Hospital, S. E. Sweitzer, M.D., Chief.

1. Dohi, K., and Dohi, S.: Zur Klinik und Aetiologie der Impetigo contagiosa, Arch. f. Dermat. u. Syph. **111**:629, 1912.

2. Lewandowsky, F.: Ueber Impetigo contagiosa s. vulgaris, Arch. f. Dermat. u. Syph. **94**:163, 1909.

3. Tachau, P.: Pemphigoid der Neugeborenen und Kinder, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1934, vol. 9, p. 34.

4. Epstein, S.: Staphylococcic Impetigo Contagiosa, Arch. Dermat. & Syph. **42**:840 (Nov.) 1940.

5. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250, 1935.

synthesis of sulfathiazole by Fosbinder and Walter [6] in 1939, it was noted that this compound was decidedly bacteriostatic for streptococci and staphyolococci. However, with little exception the reported use of sulfanilamide and sulfathiazole has been limited to their administration by mouth, intravenously or subcutaneously. It is surprising that until recently little has been published concerning the external application of these compounds and almost nothing about their use in ointments. Spink and Paine [7] used sulfathiazole in powder form, in a 1 per cent aqueous solution or suspended in cod liver oil in the local treatment of staphylococcic infections, with good results. For the treatment of impetigo, Brunsting [8] recommended an ointment containing 5 per cent sulfanilamide in olive oil and hydrous wool fat. Sams and Capland [9] used sulfathiazole in strengths of 5 to 25 per cent incorporated into "various types of pastes and ointments" but did not identify their bases. Lain [10] recommended 4 to 8 Gm. of powdered sulfanilamide to each 30 cc. of slightly warmed glycerin. Combes and Cañizares [11] used 10 per cent sulfanilamide in olive oil and hydrous wool fat.

There is a twofold advantage of topical administration of these compounds as compared with their oral administration in the treatment of local infections of the skin of streptococcic or staphylococcic origin. First, one can safely assume that the local tissue concentration of the drug will be reached with smaller amounts when the drug is applied locally than when it is given orally. Secondly, one minimizes the possibility of unpleasant toxic reactions encountered when sulfanilamide or one of its allied compounds is given by mouth.

The bacteriostatic effect of sulfanilamide on the streptococcus has well been established by Lawrence,[12] Cooper, Gross and Lewis,[13]

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6. Fosbinder, R. J., and Walter, L. A.: Sulfanilamide Derivatives of Heterocyclic Amines, J. Am. Chem. Soc. **61**:2032, 1939.

7. Spink, W. W., and Paine, J. R.: Local Use of Sulfathiazole in Treatment of Staphylococcic Infections, Minnesota Med. **23**:615, 1940.

8. Brunsting, L. A.: Treatment of Common Diseases of the Skin, Journal-Lancet **60**:438, 1940.

9. Sams, W. M., and Capland, L.: Topical Treatment with Sulfathiazole, Arch. Dermat. & Syph. **44**:226 (Aug.) 1941.

10. Lain, E. S.: Sulfanilamide in Glycerin in the Local Treatment for Pyodermas, Arch. Dermat. & Syph. **44**:257 (Aug.) 1941.

11. Combes, F. C., and Cañizares, O.: Sulfanilamide and Allied Compounds, Arch. Dermat. & Syph. **44**:236 (Aug.) 1941.

12. Lawrence, C. A.: Studies on the Effects in Vitro of New Sulfanilamide Derivatives of Heterocyclic Amines upon Micro-Organisms, J. Bact. **39**:46, 1940.

13. Cooper, F. B.; Gross, P., and Lewis, M.: Chemotherapeutic Evaluation of Sulfanilamide Derivatives of Heterocyclic Amines, Proc. Soc. Exper. Biol. & Med. **42**:421, 1939.

Neter,[14] King and Henschel[15] and many others. However, almost all investigators agree that its inhibitory action on the staphylococcus is slight. Sulfathiazole, on the other hand, has a decided bacteriostatic action on both, as was demonstrated by Lawrence,[16] Rammelkamp and Keefer[17] and others. It is for this reason that sulfathiazole was selected for our investigation. We attempted to determine whether its incorporation in an ointment base limited or destroyed its bacteriostatic effect on streptococci and staphylococci. We also tried to determine the relative importance of various bases, a fact which has been stressed on a previous occasion.[18]

## EXPERIMENTAL STUDIES

Preliminary studies demonstrated that the maximum bacteriostatic effect of sodium sulfathiazole monohydrate on cultures of Staphylococcus aureus was obtained by a 5 per cent ointment and that nothing could be gained by a higher concentration. The same was true for sulfanilamide ointments when acting on streptococcus cultures. We therefore decided to make all ointments in the strength of 5 per cent.

The agar cup-plate method[19] and the agar plate method[20] proved to be unsuitable for our purpose. We used blood agar plates which were closely streaked with Staph. aureus and beta hemolytic streptococci from a twenty-four hour broth culture. The slightly warmed ointment was applied on the plates by means of an eye dropper in amounts of 0.3 Gm.

The following ointments were tested:

1. Five per cent sodium sulfathiazole in petrolatum
2. Five per cent sodium sulfathiazole in equal parts of petrolatum and hydrous wool fat

14. Neter, E.: Comparative Study on Bacteriostatic Action of Sulfanilamide, Sulfapyridine, Sulfanilyl-Sulfanilamide and Sulfathiazole upon Enterococci, Proc. Soc. Exper. Biol. & Med. **43**:774, 1940.

15. King, J. T., and Henschel, A. F.: Bacteriostatic Effect of Sulfathiazole for Beta Hemolytic Streptococci in Tissue Culture Clots, Proc. Soc. Exper. Biol. & Med. **44**:268, 1940.

16. Lawrence, C. A.: Bacteriostatic Actions of Three Thiazol Derivatives of Sulfanilamide upon Bacteria in Broth Cultures, Proc. Soc. Exper. Biol. & Med. **43**:92, 1940.

17. Rammelkamp, C. H., and Keefer, C. S.: Sulfathiazole: Effect on Staphylococcus Aureus in Vitro, Proc. Soc. Exper. Biol. & Med. **43**:664, 1940.

18. Strakosch, E. A.: The Role of Bases in Ointments Used for Protection Against Sunlight, J. Invest. Dermat. **5**:1, 1942.

19. Ruehle, G. L. A., and Brewer, C. M.: United States Food and Drug Administration Methods of Testing Antiseptics and Disinfectants, Circular 198, United States Department of Agriculture, 1931, p. 14.

20. Ruehle and Brewer,[19] p. 12.

3. Five per cent sodium sulfathiazole in a base consisting of 6 per cent of a group of esters and alcohols of cholesterol in aliphatic hydrocarbons.[21]

4. Five per cent sodium sulfathiazole in a base consisting of fatty acid esters of diethanolamine mixed with petrolatum.[22]

5. Five per cent sodium sulfathiazole in

| | |
|---|---|
| Cod liver oil | 8.75 Gm. |
| Concentrated cod liver oil | 0.15 Gm. |
| Hydrous wool fat | 5.00 Gm. |
| Petrolatum, to make | 35.00 Gm. |

6. Five per cent sulfathiazole in the following base[23]:

| | |
|---|---|
| Wool fat | 20.0 per cent |
| White wax | 10.0 per cent |
| White petrolatum | 65.0 per cent |

7. An ointment prepared as follows[24]:

| | | |
|---|---|---|
| Sodium sulfathiazole | 5.0 Gm. | hot |
| Water | 12.5 Gm. | hot |
| Sodium alginate | 2.0 Gm. | mix |
| Water | 37.0 Gm. | mix |
| Wool fat | 8.0 Gm. | |
| Sodium chloride | 0.5 Gm. | mix |
| Water | 2.0 Gm. | mix |
| White petrolatum | 34.0 Gm. | |

8. Five per cent sodium sulfathiazole in a base[25] of:

| | |
|---|---|
| Mannide monooleate | 10 per cent |
| Ceresin wax | 10 per cent |
| Petrolatum, light | 15 per cent |
| Liquid petrolatum | 45 per cent |
| Wool fat | 20 per cent |

9. Five per cent sodium sulfathiazole in

| | |
|---|---|
| Lecithin (egg) | 5.0 Gm. |
| Petrolatum | 45.0 Gm. |
| Distilled water | 50.0 Gm. |

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21. The preparation used was aquaphor, manufactured by the Duke Laboratories Inc., Stamford, Conn.

22. The preparation used was hydrosorb, furnished to us for experimental use by the Abbott Laboratories, North Chicago, Ill.

23. Manufactured by Eli Lilly & Co., Indianapolis.

24. Ointment Base for Sulfanilamide, Queries and Minor Notes, J. A. M. A. **116**:356 (Jan. 25) 1941.

25. The base was furnished by the Wm. S. Merrell Co., Cincinnati, for experimental use.

10. Five per cent sodium sulfathiazole in

| | |
|---|---|
| Sulfanilamide | 0.5 per cent |
| Urea | 40.0 per cent |
| Karaya gum glyceride jelly | 4 per cent |

11. Five per cent sodium sulfathiazole in

| | |
|---|---|
| Sulfanilamide | 0.5 per cent |
| Karaya gum glyceride jelly | 4 per cent |

12. Five per cent sodium sulfathiazole in cetejel A [26]:

| | |
|---|---|
| Cetyl pyridinium chloride | 0.1 per cent |
| Urea | 10.0 per cent |
| Ammonium bicarbonate | 0.25 per cent |
| Allantoin | 0.5 per cent |
| Benzyl alcohol | 2.0 per cent |
| Glycerin | 11.9 per cent |
| Tragacanth | 2.36 per cent |
| Water, to make | 100.00 per cent |

13. Five per cent sodium sulfathiazole in cetejel B [26]:

| | |
|---|---|
| Cetyl pyridinium chloride | 0.1 per cent |
| Urea | 4.0 per cent |
| Ammonium bicarbonate | 2.0 per cent |
| Cycloform (isobutylparaaminobenzoate) | 0.02 per cent |
| Glycerin | 11.9 per cent |
| Tragacanth | 2.36 per cent |
| Water, to make | 100.00 per cent |

After application of the ointment, the plates were incubated at 37 C. They were turned upside down, so that the water of condensation dropped from the agar into the lid and did not interfere with the ointment or the growth of the culture. The plates were examined after six, twelve, twenty-four and thirty-six hours, for we were also interested in determining the shortest period in which inhibition of the growth took place. The width of the zone of the inhibition was measured with a millimeter rule under a hand lens. All tests were made in triplicate and were rechecked many times. The results were tabulated and are given in the accompanying table.

Similar ointments were made with sulfanilamide. The bacteriostatic action on cultures of beta hemolytic streptococci was almost identical with

26. Cetejel A and B, containing cetyl pyridinium chloride, were furnished by the Wm. S. Merrell Co., Cincinnati, for experimental use.

that of sulfathiazole. The bacteriostatic action on cultures of Staph. aureus was insignificant.

For a control we carried out similar experiments using the various ointments without sulfathiazole. The ointments had no effect with the exception of 12 and 13, which resulted in some inhibition (fig. 5), apparently due to the fact that both contained cetyl pyridinium chloride.

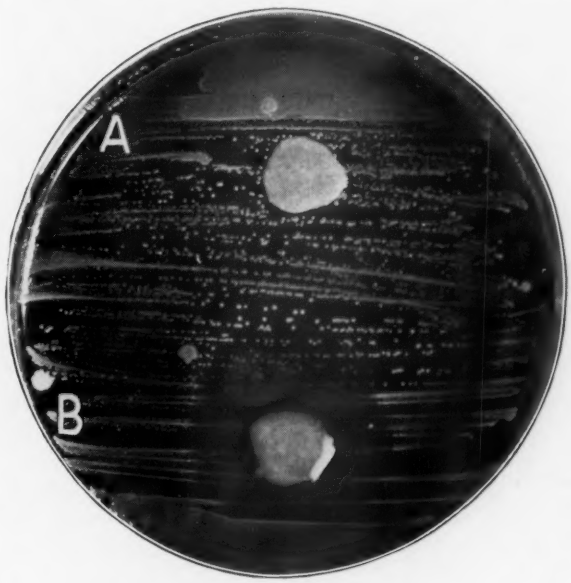


Fig. 1.—Bacteriostatic effect of ointment 2 *(A)* and ointment 3 *(B)* after twelve hours (Staph. aureus on a blood agar plate).

*Bacteriostatic Effect of Sulfathiazole in Various Ointment Bases*

| Ointment | Type of Base | Width of Zone of Inhibition, Cm.* | | | Figure |
|---|---|---|---|---|---|
| | | 6 Hr. | 12 Hr. | 24 Hr.† | |
| 1 | Hydrocarbon | 0 | 0 | 0 | 3 |
| 2 | Water in oil emulsion | 0 | 0 | 0.5 | 1 |
| 3‡ | Water in oil emulsion | 0.8 | 1.7 | 1.7 | 1 |
| 4 | Water in oil emulsion | 0 | 0.5 | 1.2 | 3 |
| 5 | Water in oil emulsion | 0.6 | 1.5 | 1.5 | 2 |
| 6 | Water in oil emulsion | 0 | 0 | 0 | 2 |
| 7 | Water in oil emulsion | 0 | 0 | 0 | — |
| 8 | Water in oil emulsion | 0 | 0.7 | 1.3 | 4 |
| 9 | Oil in water emulsion | 0 | 0.4 | 0.9 | — |
| 10 | Polysaccharide | 0.1 | 0.8 | 1.4 | 4 |
| 11 | Polysaccharide | 0.2 | 0.7 | 1.4 | 4 |
| 12 | Polysaccharide | 0.3 | 0.7 | 1.5 | 5 |
| 13 | Polysaccharide | 0.3 | 0.7 | 1.5 | 5 |

* These figures are the average of three tests of each ointment.
† There was no change after twenty-four hours.
‡ Maximum inhibition after twelve hours.

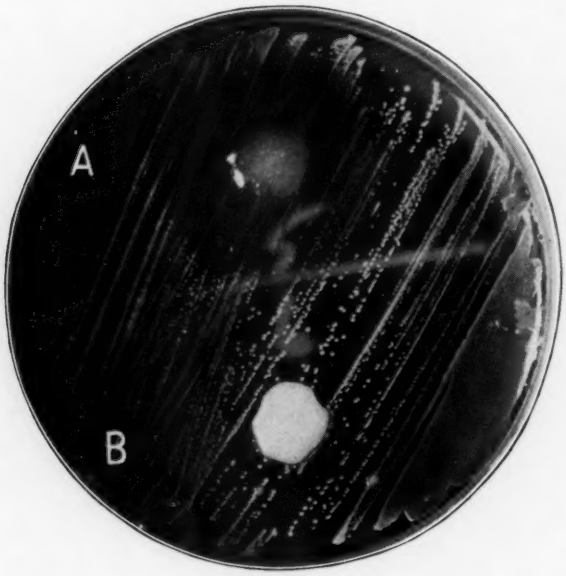


Fig. 2.—Bacteriostatic effect of ointment 5 *(A)* and ointment 6 *(B)* after twenty-four hours (Staph. aureus on a blood agar plate).

Fig. 3.—Bacteriostatic effect of ointment 4 *(A)* and ointment 1 *(B)* after twenty-four hours (Staph. aureus on a blood agar plate).

Fig. 4.—Bacteriostatic effect of ointment 10 *(A)*, ointment 8 *(B)*, ointment 11 *(C)* and control ointment *(D)* after twenty-four hours (Staph. aureus on a blood agar plate).

Fig. 5.—Bacteriostatic effect of cetejel B *(A)*, cetejel A *(B)*, ointment 13 *(C)* and ointment 12 *(D)* after twenty-four hours (Staph. aureus on a blood agar plate).

COMMENT

In selecting an ointment base, it is necessary to know the solubility of the drug to be incorporated. It should be ascertained in which medium (water, alcohol or fat) and in what proportion the drug is soluble. It is useless to incorporate in petrolatum a drug which is soluble only in water, for it is known that the drug will in most instances be liberated from the petrolatum either not at all or in amounts so insignificant that it will have no appreciable effect on the skin. Such a drug must be incorporated in an emulsion of the oil in water type or of the water in oil type or in a polysaccharide base. As a rule a water in oil emulsion penetrates the skin more readily than an oil in water emulsion or a pure hydrocarbon base and thus carries a water-soluble drug into the tissues faster. Under similar circumstances an oil-soluble drug will usually be affected in the reverse manner. But only experiments will show which type of emulsion will be the most suitable for the drug in question.

One gram of sulfanilamide dissolves in about 125 cc. of water, in about 37 cc. of alcohol or in about 30 cc. of glycerin at 25 C. The plain sulfathiazole ($C_9H_9N_3O_2S_2$) is practically insoluble in water and in alcohol and is insoluble in fats.[27] On the other hand, 1 Gm. of sodium sulfathiazole monohydrate ($C_9H_8N_3S_2O_2Na.H_2O$) dissolves in about 10 cc. of water or in about 150 cc. of 100 per cent alcohol and in approximately the same amount of glycerin at room temperature.[28] We therefore selected sodium sulfathiazole monohydrate for our studies.

A water in oil emulsion for a base appeared to be preferable for our purpose, considering the fact that sulfanilamide as well as sodium sulfathiazole monohydrate is soluble in water. Preliminary studies confirmed this choice by showing that the bacteriostatic action of sodium sulfathiazole in a water in oil emulsion was somewhat superior to that of sodium sulfathiazole in an oil in water emulsion. We then tried to find, among the different bases of the water in oil emulsion type, that base in which sodium sulfathiazole had its best bacteriostatic effect, a point of practical importance.

The results of our experiments are best seen in the table and figures and need little comment. It is, however, noteworthy that a decided bacteriostatic action was found as early as after six hours with ointment 3, in which a cholesterolized petrolatum served as a base, and with ointment 5, in which a cod liver oil ointment was used as a base. The

27. This information was given to us by L. M. Roeg, Merck & Co., Inc., Rahway, N. J.

28. These figures were obtained from E. F. Roberts, M.D., Ph.D., Lederle Laboratories, Inc., Pearl River, N. Y.

good effect of cod liver oil ointment as a base is not surprising if one considers its richness in cholesterol, an excellent emulsifier.

The addition of urea to ointments 10, 12 and 13 had no disadvantageous effect on the action of sodium sulfathiazole. It was added because it stimulates the healing of wounds, though in what strength it stimulates or inhibits wound healing is beyond the scope of this discussion. There may be an advantage in combining the use of sulfathiazole and of urea in the treatment of infected wounds.

## CONCLUSIONS

1. When sodium sulfathiazole is incorporated into suitable ointment bases, it does not lose its bacteriostatic power.

2. Sodium sulfathiazole is most rapidly effective when incorporated into bases of the water in oil type of emulsion, which are rich in cholesterol. It is likewise in these bases that the maximum effect was noted.

3. It appears that the relative mixture of fats and the emulsifier in the fats of the base are of chief importance in liberating the incorporated drug.

# ACANTHOSIS NIGRICANS ASSOCIATED WITH CARCINOMA OF THE LUNG

OSCAR L. LEVIN, M.D.
AND
HOWARD T. BEHRMAN, M.D.
NEW YORK

The diagnostic value of cutaneous lesions in the province of internal medicine is aptly illustrated by the dermatosis entitled acanthosis nigricans. This disease is uncommon, but it is so frequently associated with carcinoma of the internal organs that its positive diagnosis may be considered an indication for exploratory laparotomy.

In the adult or malignant form of acanthosis nigricans, the usual concomitant growth is a carcinoma of the stomach. The association of this pigmentary disorder with a malignant growth of the lungs has been reported in only 2 cases.

## REPORT OF A CASE

I. P., a white man aged 59, was admitted to the Beth Israel Hospital in January 1938 because of a productive cough associated with vague pains in the chest. These symptoms had been present since July 1936. In November 1937 the patient's cough had increased in intensity, and he was productive of a cupful of yellow, tenacious and frothy sputum daily. On three occasions during this time the sputum was blood streaked, but there was no hemoptysis. The pain in the chest gradually became more severe and constant and began to radiate to the left shoulder and to the axilla. During the entire year of 1937 the patient lost about 10 pounds (4.5 Kg.) and complained of increasing generalized weakness. In November he began to suffer from anorexia and constipation. The family history was irrelevant. There was no past history of carcinoma.

At the time of admission to the hospital, examination showed a chronically ill, poorly nourished man with a temperature of 99 F. and a pulse rate of 116. There were signs of a pleural effusion at the base of the right lung. The trachea was deviated to the right side of the chest, as was the heart. The heart sounds were of good quality, and the blood pressure was 170 systolic and 112 diastolic. The edge of the liver, which was tender and irregular, was palpable 8 cm. below the costal margin.

Examination of the skin revealed a flat dark brown triangular area which extended from the umbilicus to the ilioinguinal region and then spread out along the upper and inner aspects of the thighs. The apex of the triangle was above the umbilicus, and the base measured 10 cm. The area showed follicular hyperkeratosis with scaling, thickening and exaggeration of the cutaneous markings. On the left

From the Department of Dermatology, service of Dr. Oscar L. Levin, Beth Israel Hospital.

side of the chest there was dark pigmentation. There was also a pedunculated soft fibroma, about 5 cm. in size, on the abdominal wall.

Because of the cutaneous observations in association with the cough, the pain in the chest and the profuse expectoration, it was the impression of the dermatologist (O. L. L.) that the patient had a bronchogenic carcinoma with metastases to the adrenal glands.

Examination of the urine showed a 2 plus reaction for sugar but no acetone. The red blood cell count was 5,300,000; the hemoglobin amounted to 108 per

Triangular brownish black pigmentation on the abdomen associated with carcinoma of the lung.

cent; the white blood cell count was 13,650, with a differential count of 70 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes and 10 per cent monocytes. The sedimentation time was fifteen minutes. The dextrose content of the blood was 160 mg. per hundred cubic centimeters. The Wassermann reaction was negative.

On January 29 roentgen ray examination of the left side of the chest confirmed the presence of fluid in the pleural space. Thoracentesis was performed, and 2,300 cc. of a dark amber, sanguinous fluid was obtained. The fluid had a specific gravity of 1.019 and a total protein content of 64 Gm.. It contained 1,500 white

blood cells, 95 per cent of which were lymphocytes. Microscopic examination of sections of the sediment from the fluid revealed carcinoma cells.

The diagnoses at this time were: (*a*) carcinoma of the left lung, (*b*) diabetes mellitus and (*c*) acanthosis nigricans.

Permission for biopsy of the skin was not granted.

The subsequent course was uneventful, and the patient was discharged from the hospital in February.

In May the patient was admitted to the Montefiore Hospital. The physical observations at this time were similar to those made in January at the Beth Israel Hospital, with the exception of increased loss of weight. Roentgen ray examination in June 1938 showed metastatic lesions in the skull and in the pelvis.

The patient had repeated episodes of progressive dyspnea, which were relieved by thoracentesis. The fluid was usually brownish red, and on histologic examination tumor cells were found repeatedly. The condition of the patient became progressively worse, and he was made comfortable with large doses of analgesics. He died on October 11.

On autopsy the left lung was seen to be the site of an extensive carcinoma, and there were metastatic lesions in the pleura, diaphragm, liver, kidney, peritoneum, intestines and the right adrenal gland. The skin showed several lesions of acanthosis nigricans. In addition, there was a healed endocarditis of the mitral and aortic valves, coronary arteriosclerosis and generalized arteriosclerosis.

## COMMENT

Acanthosis is a benign hypertrophy of the rete mucosum, and acanthosis nigricans is an associated abnormal pigmentation with verrucous and papillomatous changes, hyperkeratosis and exaggeration of the normal markings of the skin. The earliest lesions appear in the axilla or on the neck, face or abdomen. Later the mucous membranes may become involved. The pigmentation is the result of a deposit of melanin in the basal or dendritic cells of the epidermis. The histologic picture is typical and has been well described by Montgomery and O'Leary.[1] It consists of relative and absolute hyperkeratosis and irregular acanthosis with adjacent areas of atrophy in the prickle cell layer. The papillary bodies are elongated and narrow, and there is a dense melanin pigmentation of the basal cells of the epidermis. A few chromatophores laden with pigment may be seen in the papillary bodies. The cutis shows a complete absence of any inflammatory reaction.

There are two types of acanthosis nigricans: the juvenile, or benign, and the adult, or malignant. The juvenile type is of long duration and is not associated with a fatal condition. Various toxins, metabolic and endocrine disturbances have been assigned an etiologic relation to it at

1. Montgomery, H., and O'Leary, P. A.: Pigmentation of Skin in Addison's Disease, Acanthosis Nigricans and Hemochromatosis, Arch. Dermat. & Syph. **21**: 970 (June) 1930.

one time or another. The adult type is believed to coexist with a malignant growth, chiefly of the internal organs. It is widespread, of short duration and ultimately fatal because of the associated tumor. This association of acanthosis nigricans with cancer occurs, according to Mukai,[2] who reported 218 cases, in 45 per cent of all cases. Other observers have reported even higher figures: 45.3 per cent [3] and 54.5 per cent.[4] Mukai stated that cancer, in association with acanthosis nigricans, is found in 53 per cent of the patients aged from 30 to 40 years. In patients over 40 cancer is found in 75 to 80 per cent. The organ most frequently involved is the stomach. In Mukai's series 61 per cent of the carcinomas occurred in the stomach. Masson and Montgomery [5] stated that the uterus was the next most frequently involved organ and less commonly the breast. Carcinoma of the lung is a rare coexistent neoplasm, and only 2 previous cases have been reported (Petrini Galatz [6] and Dore [7]).

## PATHOGENESIS

The physiology of pigmentary metabolism is as yet one of the unsolved mysteries of medicine. Nevertheless, there are several known facts which help shed light on the causation and development of acanthosis nigricans.

1. The adrenal glands are innervated by the splanchnic nerves, a division of the abdominal autonomic system. Nerve fibers arising in the semilunar, renal and adrenal ganglions enter the gland together with the adrenal blood vessels; some terminate directly on gland cells of the medulla, and others end in blood vessels. Secretory fibers to the cortex have not been demonstrated.

2. Pigmentary changes of the skin are commonly seen in Addison's syndrome, a disease usually caused by tuberculosis of the adrenal gland. This syndrome has also been accidentally reproduced in man by means of bilateral adrenal denervation. In one case, the operation was followed by the acute crisis of adrenal cortical insufficiency, and the skin became uniformly pigmented (Rogoff [8]).

3. In the large majority of cases of the adult type of acanthosis nigricans, the striking feature is the coexistence of some disease of the

2. Mukai, T.: Acta dermat. **14**:460, 1929.

3. Kuttner, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:276, 1926.

4. Moncorps, C., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, p. 372.

5. Masson, J. C., and Montgomery, H.: Am. J. Obst. & Gynec. **32**:717, 1936.

6. Petrini-Galatz: Bull. Soc. franç. de dermat. et syph. **20**:114, 1909.

7. Dore, cited by Mukai.[2]

8. Rogoff, J. M.: The Adrenal Medulla, in Glandular Physiology and Therapy, Chicago, American Medical Association, 1935, p. 279.

abdominal organs, usually cancer of the stomach, and especially a lesion involving the autonomic nervous system.

These facts support the theories originally advanced by Darier [9] and later concurred with by Pollitzer [10] and Wise.[11] In his "mechanico-nervous" theory, Darier stated that the cutaneous changes of acanthosis nigricans are secondary to derangements of the functions of the abdominal autonomic system induced by neoplasms of the abdominal viscera and by their metastatic growth. Darier also stated that the benign, or juvenile, type was due to the presence of such conditions as congenital malformations, peritoneal adhesions and benign growths which in some manner interfered with the abdominal autonomic nervous system.

## SUMMARY AND CONCLUSIONS

A review of the literature reveals the rare occurrence of acanthosis nigricans with pulmonary carcinoma. In the case reported here the occurrence of the lesion on the abdominal skin suggested a possible relation to abdominal carcinoma, especially of the organs involved in pigment formation and deposit. The associated pulmonary symptoms were suggestive of a primary focus in the lungs with secondary metastases to the abdominal organs, which proved to be correct on post-mortem examination. It is emphasized that apparently minor cutaneous changes, such as pigmentation, may be of value in the early diagnosis of visceral carcinoma.

2 East Fifty-Fourth Street.

9. Darier, J.: Ann. de dermat. et syph. **4**:865, 1893.

10. Pollitzer, S.: Acanthosis Nigricans: A Symptom of a Disorder of the Abdominal Sympathetic, J. A. M. A. **53**:1369 (Oct. 23) 1909.

11. Wise, F.: J. Cutan. Dis. **36**:35, 1918.

# PROPERTIES OF HUMAN SKIN REVEALED BY FLUORESCENCE MICROSCOPY

## THE NORMAL SKIN; THE VITAMIN A CONTENT OF THE SKIN

THEODORE CORNBLEET, M.D.
AND
HANS POPPER, M.D.
CHICAGO

The idea of examining the skin and its appendages and pathogenic fungi under ultraviolet rays and for their fluorescent properties is well known. Skin and epidermal appendages impart a characteristic fluorescence, as do fungous infections of the scalp, although cultures of the different fungi vary in their fluorescent properties. The microscopic examination of the skin under ultraviolet rays (fluorescence microscopy) has only rarely been employed.[1] Our interest in examining the skin under the fluorescence microscope was to find new diagnostic possibilities in the histologic study of the skin. Before we describe some of the new observations, it is appropriate to describe briefly the picture of the normal skin as shown by fluorescence microscopy. Not only the spontaneous fluorescence but also some staining reactions with fluorescent dyes were studied (fluorochromy).[2]

Our interest in these studies was also stimulated by the demonstration of vitamin A by fluorescence microscopy.[3] The characteristic, quickly

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This work was supported by a grant from the Committee on Scientific Research of the American Medical Association.

From the Department of Dermatology, University of Illinois College of Medicine, and the Graduate School of Medicine of the Cook County Hospital.

1. (*a*) Bommer, S.: Weitere Untersuchungen über sichtbare Fluoreszenz beim Menschen, Acta dermat.-venereol. **10**:391, 1929; Ueber die Fluoreszenz der elastischen Faser in der Haut, Dermat. Ztschr. **67**:319, 1933. (*b*) Baroni, P.: Contributo allo studio dei melanomi cutanei al lume di un moderno mezzo d'indagine: del microscopio a fluorescenza, Arch. ital. di dermat., sif. **9**:543, 1933. (*c*) Hamperl, H.: Die Fluorescenzmikroskopie menschlicher Gewebe, Virchows Arch. f. path. Anat. **292**:1, 1934.

2. Haitinger, M.: Fluorescenzmikroskopie, Leipzig, Akademische Verlagsgesellschaft, 1938.

3. (*a*) von Querner, F.: Der mikroskopische Nachweis von Vitamin A im animalen Gewebe. Zur Kenntnis der paraplasmatischen Zelleinschlüsse, Klin. Wchnschr. **14**:1213, 1935. (*b*) Popper, H.: The Histological Distribution of Vitamin A in Human Organs Under Normal and Pathologic Conditions, Arch. Path. **31**:766 (June) 1941.

fading green fluorescence of vitamin A is useful for detecting the presence of this substance. Previous studies have revealed that no vitamin A fluorescence can be found in the skin itself and that the presence of vitamin A in the adjacent fat tissue only is responsible for the small amounts of this vitamin found in chemical assays of the skin.[4] Because of the great importance which nowadays is attributed to vitamin A therapy of diseases of the skin,[5] a reexamination of this important point with a greater amount of material seems to be indicated. The cited studies on vitamin A fluorescence have shown that the fluorescent properties of the tissue undergo remarkable changes if kept in fixatives for a long time. Therefore only fresh sections of material, preserved not longer than twenty-four hours, have been examined in order to correct some of the older reports of fluorescence microscopic examinations in which these precautions had not been taken.

## MATERIAL AND METHODS

Specimens of the normal skin of the back were taken both with the use of local anesthetics and without them and fixed for twenty-four hours in solution of formaldehyde. Frozen sections were made in the usual manner and immediately examined. Routine histologic examinations were made. Three patients received high doses of vitamin A (2 received 150,000 U. S. P. units daily, and 1, 200,000 U. S. P. units daily) before the specimens for biopsy were taken.

A quartz mercury vapor lamp was used as a source of light. The light, rich in ultraviolet rays, was filtered through a Corning glass filter no. 584 and either through a glass cell containing a 5 per cent copper solution or through a Corning glass filter no. 428. Thus all the visible rays were cut out. A standard microscope was used with a quartz mirror. Part of the ultraviolet rays were changed by the tissue constituents to visible rays of various colors, and these newly formed fluorescent rays were obscured. The rest of the ultraviolet rays, which otherwise might have created an unpleasant sensation, were screened from the eye by an eye piece filter (Leitz ultraviolet protecting filter no. 8574 A).

The ultraviolet filter (Corning glass filter no. 584) may be changed to a ground glass filter; the section is then observed in visible light. If the section is stained with a 1 per cent solution of methylene blue for seconds, it can be studied in visible light. If the ground glass filter is changed again to the ultraviolet filter, the fluorescence may be examined.

4. Popper, H.: Vitamin A: The Distribution of Vitamin A in the Body, J. Mt. Sinai Hosp. **7**:119 (Sept.) 1940.

5. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223 (Feb.) 1941.

Many of the fluorescent phenomena, like the vitamin A fluorescence, are not influenced by staining with methylene blue and can easily be localized by alternate examination in visible and fluorescent light.

Since many tissue constituents reveal a characteristic fluorescence—i. e., the collagenous fibers a dark blue and the elastic fibers a bright gray—the orientation in an unstained section is as easy under the fluorescence microscope as in a stained section in visible light.

If Nicol prisms or polaroid films are inserted into the abbe condenser and the eye piece, the same section can be examined for double refractile properties.

Of the fluorochromes, phosphin 3 R has been employed (0.1 per cent aqueous solution for several minutes). It is a sensitive fat stain and visualizes similar fat substances as does sudan III, only in a much more distinctive way, rendering them silver white fluorescent against a brown background.

## OBSERVATIONS

According to our observations, the picture of normal skin as shown by fluorescence microscopy is as follows: The epidermis shows a dark blue fluorescence except for the keratin layer, which contrasts with a lighter blue-gray. On the surface of the epidermis, the oily secretion gives a strong fat reaction with phosphin 3R but has almost no spontaneous fluorescence, and no vitamin A fluorescence is seen. The basal layer of the epidermis is demarcated against the lighter fluorescent corium; it is a dark zone, practically not fluorescent at all (pigments often interfere with fluorescence). If large amounts of pigment are present, they are recognized as dark spots. The intercellular spaces are not recognizable. Toward the surface of the epidermis the fluorescence increases in intensity. In the corium the collagenous fibers impart a rather strong blue fluorescence, the intensity of which is proportional to the thickness of the fibers. The elastic fibers between them reveal a bright yellow-gray fluorescence, the brightest and most distinct fluorescence seen in the skin. Between the collagenous and the elastic fibers fine lipid droplets are demonstrable by phosphin 3R which are not spontaneously fluorescent. The lumens of the blood vessels stand out as dark, nonfluorescent spaces. The papillary layer shows no distinct structure, in contrast with the other parts of the corium.

The subcutaneous tissue is composed of blue fluorescent collagenous fibers and fat cells. The fat cells impart a green, slowly fading fluorescence, which is due to small amounts of vitamin A dissolved in the fat.[1]

The amounts of vitamin A fluorescence vary at different sites. Neighboring fat cells may show various degrees of the vitamin A fluorescence. Usually the smaller the fat droplets are, the brighter is the green, fading vitamin A fluorescence which they impart. In specimens of skin

from patients who received high doses of vitamin A, the fat fluorescence was slightly but not decisively increased. After fading of the vitamin A fluorescence a darker green fluorescence remains, which also varies in

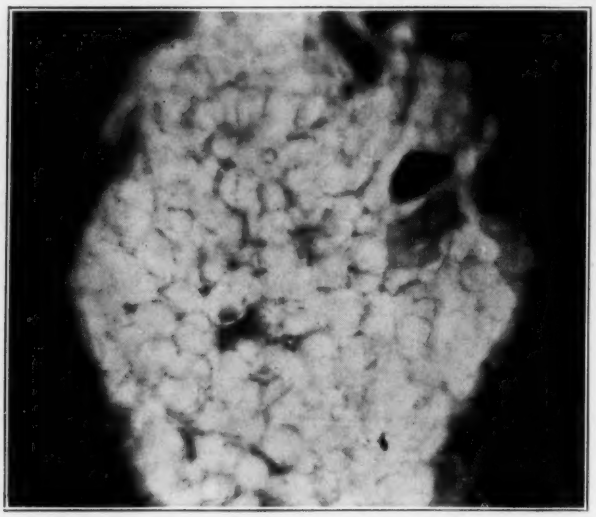

Fig. 1.—Vitamin A fluorescence of fat cells.

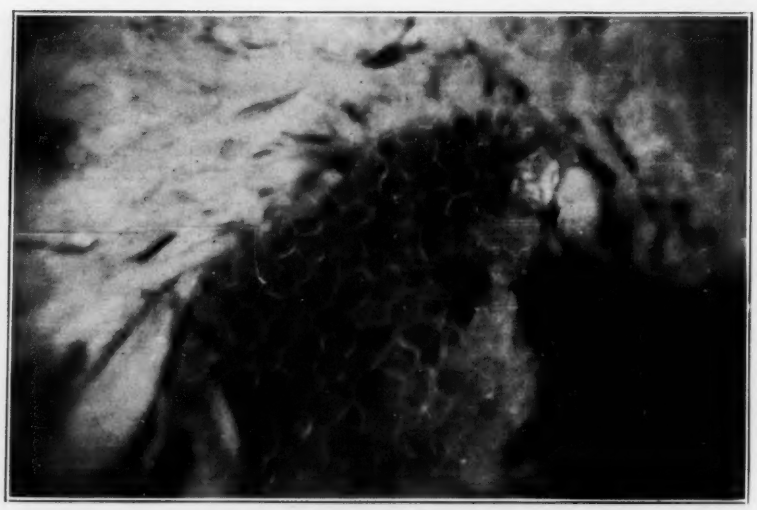

Fig. 2.—Fat cells after fading of vitamin A fluorescence and strong blue fluorescence of the dense connective tissue in the neighborhood.

intensity at various sites. This secondary fluorescence may be due to fat pigments, since it disappears after treatment with acetone. With phosphin 3R the fat cells impart a strong silver white fluorescence.

Fig. 3.—The cutis, showing strong bluish fluorescence of collagen fibers and brighter gray fluorescence of the elastic fibers. The epidermis is practically not fluorescent.

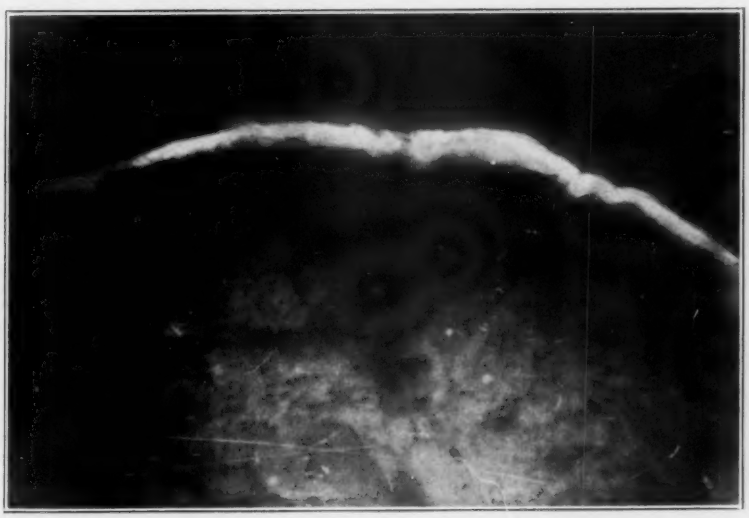

Fig. 4.—Strong silver white fluorescence of the surface with phosphin 3 R stain. Fine lipid droplets in the cutis give a diffuse white fluorescence.

Hair follicles show in their lumens a degree of luminescence comparable to that seen at the surface of the epidermis between follicles. The epidermal cells are dark, in keeping with what is found in the epidermis generally. The hair within the follicles also is dark, except at the surface of the hair as seen in a silhouette view. Some hairs infected by fungus emit a brilliant green. The surface of nail scrapings shows a slight luminescence, but even thin bits of nail are opaque. A more detailed description of hair and nails as examined separately under the fluorescence microscope was given by Hamperl.[1e]

The oil glands reveal a grayish, ultraviolet, stable fluorescence. The degree of luminescence of the oil glands increases toward the interior of each acinus. The cavity of the acinus shows up rather brightly. The fluorescence disappears after treatment of the sections with lipid solvents. The sebaceous glands show a bright fluorescence after being stained with methylthionine chloride U. S. P. (methylene blue) and especially with phosphin 3R. No vitamin A fluorescence is present. In epithelial layers of the sweat gland there are fine gold-red fluorescent granules which do not show up with phosphin 3R. Their fluorescence is only slightly changed by acetone. These bright-appearing granules are not seen in the ducts.

The apocrine glands in the axilla show in their epithelium irregularly shaped, rust brown bodies, sometimes of large size, pointing into the lumen of the gland. The fluorescence is not destroyed by attempts to dissolve the responsible material with acetone. The quality of the color resembles that from "wear and tear" pigment.

## COMMENT

Fluorescence microscopy of the normal skin reveals various details which may possibly be helpful in the analysis of pathologic specimens. Vitamin A fluorescence is found only in the adjacent fat tissue and not in the epidermis itself. The other lipids of the skin (oil glands and surface fat) are free of vitamin A. The feeding of large amounts of vitamin A does not produce storage of vitamin A in the epidermis. This is the more interesting since the epidermis is one of the first sites of the body to react to a deficiency of vitamin A.[6] Some persons think that the pathologic changes of the skin with hyperkeratinization are the first clinical signs of vitamin A deficiency.[7] Since vitamin A is absent from the epidermis under normal conditions and even after the feeding of large quantities of vitamin A, it appears that the influence of its metabolism

6. Wolbach, S. B.: The Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. **108**:7 (Jan. 2) 1937.

7. Lehman, E., and Rapaport, H. G.: Cutaneous Manifestations of Vitamin A Deficiency in Children, J. A. M. A. **114**:386 (Feb. 3) 1940.

on the skin must be mediated from some other site. The reduced storage of vitamin A somewhere else (liver?) in vitamin A deficiency or its reduced metabolism may be the cause of the changes found in the skin. Previous studies on human material [3b] and experimental animals [4] showed that epithelium from other organs, such as the bronchi, gastrointestinal tract or urinary tract, is similar to that of the skin in that it is lacking in fluorescent properties and is sensitive to vitamin A metabolism.

SUMMARY

The picture of normal skin as shown by fluorescence microscopy is described. Vitamin A fluorescence is found only in the fat cells and not in the epidermis, although the latter is sensitive to vitamin A deficiency. It is absent from the epidermis even after feeding of high doses of vitamin A. Fluorescence microscopy is presented as another tool which may be of some help to the dermatologist.

310 South Michigan Avenue.

1825 West Harrison Street.

# WARTS

## A STATISTICAL STUDY OF NINE HUNDRED AND TWENTY-ONE CASES

R. H. RULISON, M.D.
NEW YORK

This article is intended to clear up a few scattered points in the natural history of warts and to ascertain the types of therapy in common use today.

Warts are autoinoculable and transmissible.[1] The incubation period after experimental inoculation varies from one to twenty-one months and averages four months. It has been demonstrated that infection by a virus causes warts, and this observation has been confirmed by a number of investigators.[2]

Warts occur not only in human beings but in cattle, dogs and rabbits.[3] The viruses causing warts are, in general, species specific; hence it is not possible to acquire warts from contact with an infected animal.

Wart viruses are not only species specific but also epitheliotropic; that is, they invade only cells of epithelial origin.

In rabbits, two separate viruses have been isolated, one of which causes cutaneous warts [4] and the other warts of the mucous membranes.[5] Immunity to reinfection due to the production of antibodies occurs in rabbits after the development of either type of wart, but this immunity does not apply to inoculation with the other virus.

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1. Variot, G.: J. de clin. et de thérap. inf. **2**:893, 1894. Jadassohn, J.: Verhandl. d. deutsch. dermat. Gesellsch. (1895) **5**:497-512, 1896. Lanz, O.: Deutsche med. Wchnschr. **25**:313, 1899. Juliusberg, M.: Arch. f. Dermat. u. Syph. **64**:163-174, 1903.

2. Serra, A.: Gior. ital. d. mal. ven. **43**:11-42, 1908. Wile, U. J., and Kingery, L. B.: The Etiology of Common Warts: Preliminary Report of an Experimental Study, J. A. M. A. **73**:970-972 (Sept. 27) 1919. Templeton, H. J.: Long Incubation Period of Warts, Arch. Dermat. & Syph. **32**:102-103 (July) 1935.

3. Findlay, G. M., in Andrewes, F. W.; Arkwright, J. A., and others: A System of Bacteriology in Relation to Medicine, Medical Research Council, London, His Majesty's Stationery Office, 1930, vol. 7, p. 252.

4. Shope, R. E.: J. Exper. Med. **58**:607-624, 1933. Rous, P., and Beard, J. W.: ibid. **60**:701-722, 1934. Beard, J. W., and Rous, P.: Proc. Soc. Exper. Biol. & Med. **33**:191-193, 1935.

5. Parsons, R. J., and Kidd, J. G.: Proc. Soc. Exper. Biol. & Med. **35**:441-443, 1936.

It is not known whether separate viruses cause the different types of warts that occur in man. Experimentally produced verrucae vulgares resemble smooth flat warts for some months after their appearance and become rough only at a later period.

Warts may persist for many years or may disappear spontaneously. There is no uniformly successful treatment, and published reports of results obtained by one author do not hold good for another who tries the method advocated.

The incidence of warts in human beings has never been determined. Patients with warts represent between 1.5 and 4 per cent of patients applying for dermatologic treatment, and this percentage seems to be increasing.[6]

The five varieties of warts which occur in man are verruca vulgaris, verruca plantaris, verruca plana juvenilis, verruca filiformis and verruca acuminata. Because of its comparative rarity verruca acuminata is

TABLE 1.—*Frequency of Different Types of Warts*

| Type of Wart | Cases | |
|---|---|---|
| | Number | Per Cent |
| Verruca vulgaris | 659 | 71.6 |
| Verruca plantaris | 177 | 19.2 |
| Verruca plana juvenilis | 60 | 6.5 |
| Verruca filiformis | 25 | 2.7 |
| Total | 921 | |

omitted from this study.[7] Seborrheic and senile keratoses are also omitted, since they are not due to virus infection. Verruca vulgaris and verruca plantaris are separated in this analysis, although some authorities believe that the latter is only a common wart having a changed appearance due to pressure.

This paper deals with 921 cases of verrucae in which adequate histories were obtained. In 49 of these cases there were second attacks which occurred after a period so long that they could not be considered recurrences. The available records, therefore, were obtained from 872 persons. One fifth of these were private patients, and the others were dispensary patients.[8]

The comparative frequency of the four types of warts studied is shown in table 1.

6. Osborne, E. D., and Putnam, E. D.: Radiology **16**:340-345, 1931.

7. The diagnosis of venereal warts was made only 32 times in over a quarter of a million new cases observed in the ten year period 1925 to 1934 at the New York Skin and Cancer Hospital.

8. About 350 dispensary patients were from the service of Dr. Hans J. Schwartz at the New York Hospital and the same number from the service of Dr. J. Gardiner Hopkins at the Vanderbilt Clinic.

Warts may be either single or multiple. Chart 1 shows the comparative frequency of single and multiple lesions in the cases of the four types of warts studied. Single warts composed 46.9 per cent of the lesions in the 750 cases of all types. Single verruca vulgaris occurred in 47.4 per cent of this group (523 cases). Single verruca plantaris occurred in 57.9 per cent of that group (164 cases). In all cases of verruca plana juvenilis the warts were multiple (45 cases), and in 50 per cent of those of verruca filiformis the lesions were single (18 cases).

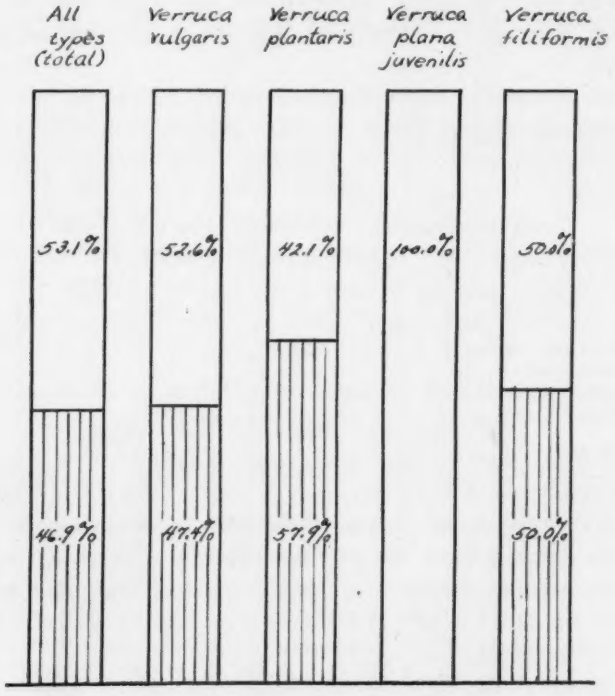


Fig. 1.—Incidence of single (lined spaces) and multiple (empty spaces) warts in 750 cases.

The distribution relative to age is shown in chart 2. The age group from 16 to 20 shows the highest incidence of warts of all types. Verruca vulgaris and verruca plantaris are also most frequent in this age group. Verruca plana juvenilis is most commonly found between the ages of 5 and 20, and the incidence of verruca filiformis is greatest in the age group from 26 to 30. Verruca plana juvenilis is not limited to the adolescent group but occurs in patients up to 40 years of age.

Chart 3 indicates the duration of the warts at the time the patient first sought treatment. Treatment is applied for most frequently between

one and three months after the wart is first noticed. Some patients do not seek treatment for many years. Single warts are more frequently found in patients applying for treatment less than six months after the wart was noticed. The ratio of multiple to single warts increases rapidly in patients who apply for treatment after the warts have been present six months or longer.

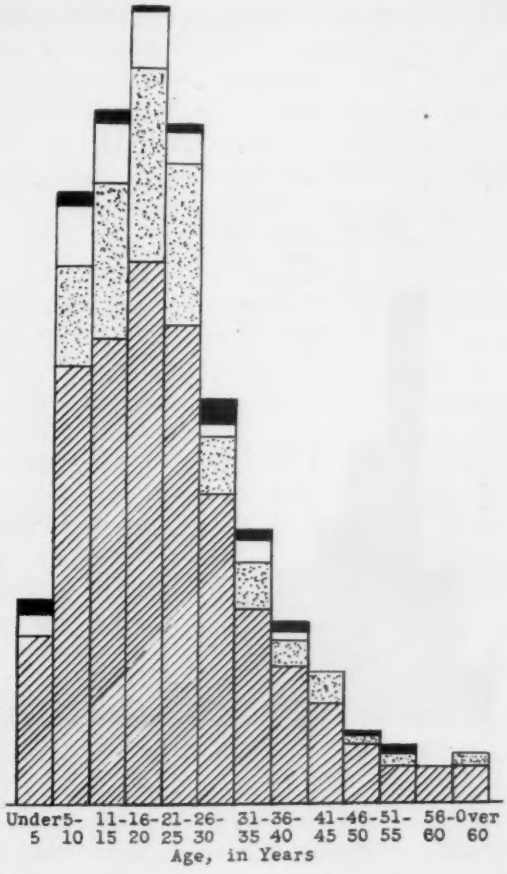


Fig. 2.—Nine hundred and twenty-one patients with warts classified according to type of wart and age of patient when wart appeared. Spaces with diagonal stripes indicate verruca vulgaris (659 cases); spaces with dots, verruca plantaris (177 cases); empty spaces, vreruca plana juvenilis (60 cases), and filled-in spaces. verruca filiformis (25 cases).

Of 872 persons, 373 (42.7 per cent) were males and 499 (57.2 per cent) were females. The high percentage of females in this series of cases was surprising.[9] It was expected that the incidence of warts in

9. The statistics of the New York Skin and Cancer Hospital over a ten year period (1925 to 1934) show that 53.3 per cent of warts occurred in females.

males would be considerably higher than in females, because breaks in the surface of the skin from trauma are more frequent in males. The suggestion was made that women are more distressed by warts than men and apply for treatment more frequently. However, analysis of the duration of warts before applying for treatment in the two sexes shows that females do not apply for treatment sooner than males; so it appears that the incidence of warts in females is somewhat greater than in males.

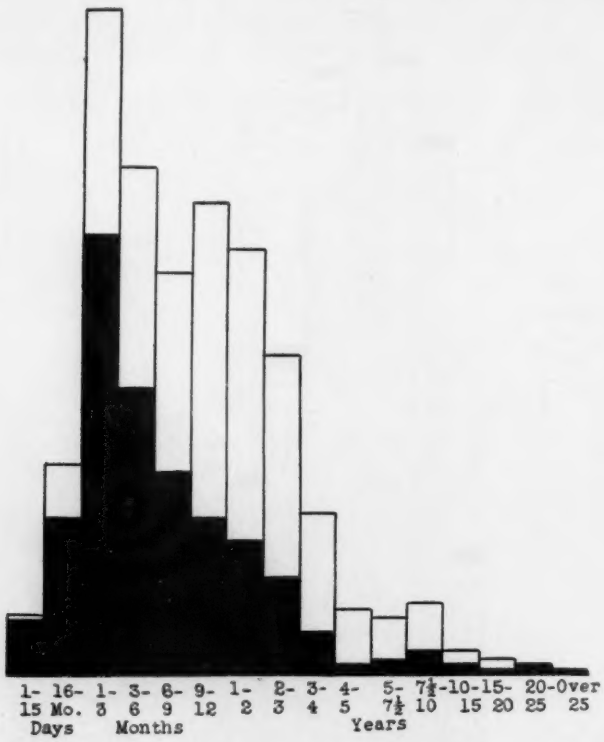


Fig. 3.—Duration of warts at time patient sought treatment; single (filled-in spaces) and multiple (empty spaces) warts in 750 cases of all types of warts.

Histories of the family incidence of warts were obtained from 160 persons. Sixty-seven of these had never had warts and reported that warts had occurred in other members of their families in 13 instances; the family incidence of warts in this group was 19.4 per cent. Ninety-three persons had warts, and warts had occurred in other members of their family in 40 instances; the family incidence of warts in this group was 43 per cent. The number of cases in which information on this point was obtained is too small to allow any definite conclusion, but analysis suggests the possibility that some families have relatively higher resistance to infection than others.

Of 476 persons with verruca vulgaris, 129 applied for treatment three months or less after the warts were first noticed. The percentage of single warts in this group was 70. Ninety-six had had their warts for from three to six months. The percentage of single warts in this group was 50. Two hundred and fifty-one had had warts for more than six months. The percentage of single warts in this group was 36.7.

The aforementioned figures are of interest in reference to antibody production. Warts occurring in animals are known to cause production of antibodies, and it is assumed that the same is true of human beings. The antibodies do not cause the disappearance of the warts, but they provide immunity for the animal's normal cells, so that reinoculation fails to cause warts.[10] The only reference in the literature to immunity in human beings occurs in Findlay's article.[3] He found that after inoculating himself with three crops of warts he became immune to further inoculations. How long this immunity lasted is not known.

The increasing percentage of multiple warts in man, as time passes, suggests that if antibodies are produced in the human body, they are insufficient, for many months, to protect normal cells from the development of new warts.[11] It also seems that multiple warts last longer than single warts and that in second attacks multiple warts are much more frequent than in first attacks.

One might assume that the more warts, the greater would be the production of antibodies, but this study does not support this assumption. It seems more probable that some persons fail to produce antibodies.

A male patient aged 18, shown at a meeting of the New York Academy of Medicine Section of Dermatology and Syphilis in 1934,[11] had thousands of warts, involving the head, trunk and all extremities. The duration of this condition was two years.

## SPONTANEOUS DISAPPEARANCE OF WARTS

No satisfactory explanation has yet been offered for the spontaneous disappearance of warts. It is known that in animals (and probably in human beings) infection with the wart virus is followed by the production of antibodies, but research workers do not think that this antibody production explains spontaneous disappearance.

Virus diseases are intracellular, and antibodies are unable to penetrate cell membranes. Antibodies are useful in protecting normal cells, thus limiting extension of the process and protecting from reinfection, but not in neutralizing or destroying virus already present.

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10. (*a*) Rivers, T. M.: Bull. New York Acad. Med. **17**:245-258, 1941. (*b*) Parsons and Kidd.[5] Footnote 4.

11. Harris, J. H.: Verruca Vulgaris and Verruca Plana, Arch. Dermat. & Syph. **31**:271-272 (Feb.) 1935.

Many virus diseases are self limited, and recovery has been explained by assuming that the particular virus dies when the cells which it attacks are unsatisfactory hosts or when the virus rapidly causes death of infected cells.

Rivers [10a] made the following observations:

> As a result of the close relationship between viruses and their host cells, one of three things or a combination of these three things may occur. Rapid growth of a virus may cause immediate death of infected cells, or multiplication of the virus may first stimulate the cells and then destroy them, or, finally, the virus may act in such a manner that only stimulation of cells takes place. As one examines pathological tissues from virus diseases one sees that the things just mentioned have happened. In yellow fever, Rift Valley fever and foot-and-mouth disease the rapid growth and explosive action of the viruses lead to a picture of necrosis. In smallpox, fowl pox, vaccinia, chickenpox, and certain other virus diseases one sees early in the development of lesions only stimulation of infected cells which accounts for the formation of papules; later the stimulated cells making up the papular eruptions undergo destruction producing pustules or vesicles. Finally, in such conditions as Rous' sarcoma of chickens, Shope's papilloma, and warts, stimulation of cells is a prominent, if not the only, feature of the pathological picture.

The previous analysis of 476 cases indicated that satellite warts were still appearing six months after the first wart was noticed. The inference seems warranted that antibody production in human beings must be slow. In this series of cases, 63 were selected as being instances of spontaneous disappearance. Twenty-three of these cases were separated because of self treatment or because of circumstances which might be considered a form of psychotherapy. This leaves 40 cases for analysis (table 2). The 23 excluded cases are analyzed in tables 3, 4 and 5.

The average age of the patients when the history was taken was 30.6 years. The average age of the patients at the first appearance of the warts was 13.9 years. Twenty-three were males and 17 females. In 18 of the 40 there was no later attack of warts. The warts were single in 12 and multiple in 6 of this group. The average age of these 18 patients when warts first appeared was 12.6 years.

In 22 patients a second attack was experienced. Of these patients the warts were single in 6 and multiple in 16 in the first attack. The average age of this group when warts first appeared was 16 years. The average age of this group when the second attack occurred was 25.7 years.

In 4 of these 22 patients, a third attack occurred. In 3 of them the warts were multiple; in 1 the number of warts in the third attack was not stated. The average age of these 4 patients at the third attack was 30.6 years.

The average duration of the first attack was two and twenty-eight hundredths years. The average duration of the second attack was three and thirteen hundredths years.

In the first attack the warts were single in 19 and multiple in 21 patients. Of 20 of the 40 patients who had second attacks, 2 had single and 18 multiple warts.

TABLE 2.—*Forty Cases in Which Warts Disappeared Spontaneously*

| | | First Attack | | | | | Second Attack | | | | | Third Attack | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number | Sex | Age | Warts, Single or Multiple | Type of Wart * | Duration, Years | Free Period, Years | Age | Warts, Single or Multiple | Type of Wart | Duration, Years | Second Free Period, Years | Age | Type of Wart | Warts, Single or Multiple | Duration, Years | Third Free Period, Years | Warts Still Present | Present Age | No More Warts |
| 1 | M | 5 | M | VV | 2 | 25 | 32 | M | VV | 8 | 14 | .. | ... | .. | .. | .. | .. | 54 | + |
| 2 | M | 6 | M | VV | 2 | 10 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 18 | + |
| 3 | M | 6 | M | VV | ? | ? | 7 | M | VP | .. | .. | .. | ... | .. | .. | .. | + | 7 | .. |
| 4 | M | 6 | M | VV | 1 | 17 | 24 | M | VV | 1 | 3 | .. | ... | .. | .. | .. | .. | 28 | + |
| 5 | M | 7 | S | VV | ¼ | 15 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 22 | + |
| 6 | F | 7 | S | VV | 5 | 11 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 23 | + |
| 7 | F | 7½ | M | VV | 7 | 5 | 19½ | M | VV | ½ | (Treated; cured) | .. | .. | .. | .. | .. | .. | 21 | + |
| 8 | M | 7½ | S | VV | 4½ | 34 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 46 | + |
| 9 | M | 7½ | M | VV | ½ | 31 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 39 | + |
| 10 | F | 7½ | S | VV | 4½ | 15 | 27 | M | VV | .. | .. | .. | ... | .. | .. | .. | + | 27 | .. |
| 11 | F | 8 | M | VV | ½ | 21 | 29 | M | VV | (Treated) | | 43 | VV | — | .. | .. | + | 43 | .. |
| 12 | F | 9 | M | VV | 2 | 33 | 44 | M | VV | (Treated) | | .. | ... | .. | .. | .. | .. | 45 | ? |
| 13 | F | 10 | S | VV | 1 | 6 | 17½ | M | VV | 2½ | .. | .. | ... | .. | .. | .. | + | 20 | .. |
| 14 | F | 10 | M | VV | 3 | 3 | 16 | M | VP | 5 | .. | .. | ... | .. | .. | .. | + | 21 | .. |
| 15 | M | 10 | M | VV | 2 | 2½ | 14½ | M | VV | 2½ | .. | .. | ... | .. | .. | .. | + | 17 | .. |
| 16 | M | 11 | S | VV | 1/12 | 46 | 57 | S | VV | ⅛ | (Treated) | ... | .. | .. | .. | .. | .. | 57 | .. |
| 17 | F | 11 | M | VV | 4 | 3 | 18 | M | VPJ | 4½ | 6 | 28½ | VF | M | .. | .. | + | 33 | .. |
| 18 | M | 11 | S | VV | ½ | ⅓ | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 12 | + |
| 19 | M | 12 | S | VV | 4½ | 18 | 32 | M | VV | .. | .. | .. | ... | .. | .. | .. | + | 32 | .. |
| 20 | M | 13 | M | VV | 4 | 6 | 23 | M | VV | (Treated; cured) | | 24 | VV | M | (Treated) | | .. | 24 | .. |
| 21 | F | 13 | M | VV | 7 | 7 | 27 | M | VV | .. | .. | .. | ... | .. | .. | .. | + | 28 | .. |
| 22 | M | 14 | S | VV | 1 | 10 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 25 | + |
| 23 | F | 14½ | M | VP | 1 Tr | 9 | 24½ | M | VV | 1— | 2 | 27 | VV | M | .. | .. | + | 27 | .. |
| 24 | F | 15 | S | VV | ? | 5 ? | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 20 | + |
| 25 | M | 15 | M | VV | 8 | ? | ? | S | VV | ? | (Treated) | ... | .. | .. | .. | .. | .. | 29 | .. |
| 26 | M | 15 | S | VV | ½ | 2 | 17½ | M | VPJ | .. | .. | .. | ... | .. | .. | .. | + | 18 | .. |
| 27 | F | 15½ | S | VV | ? | 8 ? | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 24 | + |
| 28 | M | 16 | M | VV | 1 | 5 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 22 | + |
| 29 | M | 16 | S | VV | ½ | 6½ | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 23 | + |
| 30 | F | 17 | M | VV | ½ | 4½ | 21 | M | VV | ? | .. | .. | ... | .. | .. | .. | + | 21 | .. |
| 31 | M | 18 | M | VV | ⅔ | 24 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 43 | + |
| 32 | M | 19 | S | VV | 1½ | 45 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 65 | + |
| 33 | F | 21 | M | VV | 1 Tr | 5 | 27 | M | VV | ¼ | 7 | .. | ... | .. | .. | .. | .. | 34 | + |
| 34 | M | 21½ | M | VV | 1 (1) | Second wart still present | | | | | | .. | ... | .. | .. | .. | + | 28 | .. |
| 35 | F | 22 | M | VV | 4½ | 20 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 46 | + |
| 36 | F | 25 | S | VV | 1 | 9 | 35 | ? | ... | .. | .. | .. | ... | .. | .. | .. | + | 35 | .. |
| 37 | M | 26 | S | VV | 2 | 6 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 34 | + |
| 38 | M | 26 | S | VV | ¼ | 12 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 38 | + |
| 39 | M | 26 | M | VV | ¾ | 13 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 39 | + |
| 40 | F | 28 | S | VV | ¼ | 8 | .. | .. | ... | .. | .. | .. | ... | .. | .. | .. | .. | 36 | + |

* VV indicates verruca vulgaris; VP, verruca plantaris; VPJ, verruca plana juvenilis; VF, verruca filiformis.

The free period between the first and the second attack averaged eleven and eight-tenths years and between the second and the third attack four and nine-tenths years. In the first attack the duration of single warts averaged one and seven-tenths years (16 cases). In the first attack the duration of multiple warts averaged two and seven-tenths years (19 cases).

Concerning the age at which the first attack of warts occurred, of the youngest 20 patients 8 had single and 12 multiple lesions, and of the oldest 20 patients 10 had single and 10 multiple warts.

Two sisters and a brother and sister were included in this group of 40 patients. This leaves thirty-eight families to be considered. In sixteen of them no record of familial incidence could be obtained. Of 22 patients who had spontaneous disappearance of warts, 11 gave a history of warts in other members of the family, and 11 knew of no other cases in their families.

Although the number of cases is small, these 40 histories were carefully checked, and a study of the group at least suggests some hypotheses. It appears that the average duration of untreated warts is between two and three years in the first attack and that warts resulting from a later infection last longer than those in the first. Perhaps the question whether warts are single or multiple is not important. However, one would expect more antibodies to be produced by persons with multiple than with solitary warts. If this were true, permanent or long-continued immunity should follow recovery from multiple warts. Analysis of the 40 cases suggests that multiple warts occur in persons having little or no natural immunity or in whom antibodies fail to develop, whereas single warts develop in persons with relatively high natural immunity or who produce large amounts of antibodies promptly.

## TREATMENT

Many methods of treatment are in use. It is a truism that when this is the case none is perfect. Warts are self limited in many persons. Ideal treatment would remove them quickly, painlessly and permanently, without scarring and without danger of infection, and would be effective in every case. No such treatment is available.

*Local Treatment.*—Surgical excision, curettage and destruction by heat, cold, caustics and keratolytics comprise a therapeutic group which breaks the skin and opens the way for infection. These methods are uncomfortable; healing is often slow, and scarring often follows. The procedures are not of practical use when a large number of warts are present.

Another therapeutic group includes methods based on pressure and the exclusion of air. Examples are: the application of collodion, elastoplast or silver nitrate and superficial desiccation.[12] Claims that therapy based on these procedures is effective are made from time to time. There is no agreement that these claims are warranted.

12. Sutherland-Campbell, H.: Common Warts: Effective Treatment, Arch. Dermat. & Syph. **30**:821-822 (Dec.) 1934.

Other methods of local treatment involve the repeated application of a large and diverse list of substances which are thought to have a specific action. In this group are milkweed juice, celandine juice and lemon juice, which are recommended by the laity, and fluidextract of thuja, solution of potassium arsenite U. S. P., castor oil and oil of cinnamon, sometimes ordered by physicians. None of these applications are generally accepted as efficacious.

TABLE 3.—*Eight Cases of Warts in Which Lay Treatment (Nontraumatic) Was Used*

| Number | Present Age | Sex | Age at First Attack | Warts, Single or Multiple | Duration Before Treatment, Yrs. | Duration of Treatment | Number of Treatments | Treatment Used | Recurrence | New Attack | Free Period, Yrs. | No More Warts |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 33 | F | 6 | M | 1/6 | ? | ? | Father spit tobacco juice on warts | 0 | 0 | 27 | + |
| 2 | 47 | F | 8 | M | 7/12 | ? | ? | Mother advised licking warts on rising in morning | 0 | 0 | 38 | + |
| 3 | 43 | F | 12 | S | ½ | 6 wk. | ? | Hindu advised sucking wart and touching it with tongue | 0 | 0 | 30 | + |
| 4 | 29 | M | 13 | M | 1 | — | 1 | Rubbed warts with salt pork rind (customary among Swedish people) | 0 | + | 14 | — |
| 5 | 46 | F | 6 | M | ? | ? | ? | Friend of mother suggested the application of axle grease | 0 | 0 | 40 | + |
| 6 | 39 | F | 7 | M | 2 | 1¾ yr. | — | Dandelion juice applied often | 0 | 0 | 30 | + |
| 7 | 44 | M | 8 | M | Several wk. | 4 days | 4 | Applied milkweed juice daily at suggestion of playmates | 0 | 0 | 36 | + |
| 8 | 21 | M | 9 | M | 2 | 2 mo. | 2 | Soaked hand in lemon juice twice; in later attack used vinegar and water successfully; still has one verruca vulgaris on right little finger | 0 | ++ | 10 | — |

*Roentgen Irradiation and Radium Therapy.*—Roentgen rays and radium are frequently used. Different authors report widely varying percentages of cures. No agreement exists as to dose, filtration, intervals between treatments or number of treatments. Most dermatologists of wide experience agree that a fairly large percentage of warts are resistant to radiation therapy and that there is no way of identifying the resistant wart in advance of treatment. MacKee and Cipollaro,[13] after long experience, stated that only 50 per cent of warts respond to radiation therapy.

13. MacKee, G. M., and Cipollaro, A. C.: Bull. New York Acad. Med. **11**:383-391, 1935.

In cases in which cure is obtained irradiation has many advantages: The treatment is painless; reactions are usually mild; the skin is not broken; dressings are unnecessary, and the warts disappear without scarring. The disadvantages are: long treatment of radioresistant warts without benefit, the possibility of cutaneous sequelae, the changes that occur in the deeper tissues which seem to interfere with repair when later surgical intervention has been found necessary, delayed recurrences in situ and the difficulty in determining when adequate treatment has been given. Figures showing percentages of cures by this method need careful analysis. Often warts are under treatment by irradiation for many months. While this keeps the patient under observation, the total

TABLE 4.—*Eight Cases of Warts in Which Self Treatment (Traumatic) Was Used*

| Number | Present Age | Sex | Age at First Attack | Duration Before Treatment, Yrs. | Duration of Treatment | Method Used | Treatment Failure or Success | Recurrence | New Attack | Free Period, Yrs. | No More Warts |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | M | 10 | 1 | — | Accidentally knocked wart off..... | S | 0 | 0 | 20 | + |
| 2 | 48 | M | 12 | ? | — | "Picked it out"..... | S | 0 | 0 | 36 | + |
| 3 | 41 | F | 14 | ½ | — | "Cutting with manicure scissors and digging with fingernails" | S | 0 | 0 | 26 | + |
| 4 | 24 | M | 15 | 1 | — | "Bit it off" (once)..... | S | 0 | 0 | 8 | + |
| 5 | 24 | M | 15 | 4½ | — | "Biting warts—after 3 unsuccessful tries the fourth was successful" | S | 0 | 0 | 4½ | + |
| 6 | 32 | M | 18 | ? | — | "Picked if off and no recurrence" | S | 0 | 0 | 14 | + |
| 7 | 41 | M | 21 | ½ | 3 wk. | Touched wart with heated lead pencil; went away in a few weeks | S | 0 | 0 | 19 | + |
| 8 | 56 | M | 25 | ½ | — | Knocked wart off while rigging sail | S | 0 | 0 | 30 | + |

duration of treatment is so much longer than is usual with other forms of therapy that the chance of spontaneous cure is increased and tends to increase the apparent cures.

*Internal Medication.*—This method has its advocates. Administration may be either by mouth or by injection. Examples are: oral administration of protiodide of mercury [14] and of magnesium sulfate and injections of a bismuth compound [15] or of one of the arsphenamines.

14. Ziegler, A.: München. med. Wchnschr. **68**:332, 1921.

15. Lurie, S. A.: Verruca Vulgaris (Palmar and Plantar): Treatment by Intramuscular Injections of Bismuth Salicylate, Arch. Dermat. & Syph. **26**:95-97 (July) 1932. Lunsford, C. J.; Thomson, R. R.; Binkley, G. W., and Fox, D. S.: California & West. Med. **39**:385-388, 1933.

Here again different authors report great variations in percentage of cures. In most instances, controls are lacking, and the duration of the warts, of treatment and of subsequent observation is inadequately stated.

*Vaccine Therapy.*—Biberstein [16] has written about vaccine therapy of warts. He used autolysates made from human warts and from cattle warts. He controlled his work by injections of extract of normal skin. He reported cures in between 50 and 70 per cent of cases of verruca vulgaris and in 85 to 90 per cent of cases of verruca plana juvenilis. The duration of treatment (by inference) was from five to ten weeks, and the period of subsequent observation was not definite. Other investigators have failed to obtain similarly good results by this method, and Findlay [8] stated that warts of one species are not transferable to another and that their extracts have no curative effect in different species.

*Psychotherapy.*—A further difficulty in assaying therapeutic efficiency arises from claims for the curative value of suggestion.[17] Warts have disappeared soon after some form of psychotherapy in many instances. This is borne out not only by folklore, common report and statements in the lay press but also in medical literature under the names of famous dermatologists. The enthusiasts for this form of treatment feel that many cures credited to other methods are often the result of unintentional psychotherapy. They go so far as to say that mere refusal to treat a wart constitutes suggestion therapy.[17a]

Here, again, data concerning the duration of treatment and the promptness of cure, as well as other data desirable in deciding the question of the actual percentage of cures obtained, are scanty. Controls have been watched only in 1 instance, and, logically, the mere observation of these cases may be considered a form of suggestion.

Memmesheimer and Eisenlohr [17b] followed 140 patients with warts for six months. Seventy were treated by psychotherapy, and 70 were untreated, as controls. At the end of six months it was found that 17 treated patients and 20 untreated patients were cured.

If psychotherapy were successful in a high percentage of cases it would be ideal. However, the reported percentages of cures are not high and vary with individual physicians. Perhaps the most startling feature of the reports of cures by this method is the rapidity of the

16. Biberstein, H.: Klin. Wchnschr. **4**:638, 1925; **11**:1021-1025, 1932.

17. (*a*) Bloch, B.: Klin. Wchnschr. **6**:2271-2275 and 2320-2325, 1927. (*b*) Memmesheimer, A. M., and Eisenlohr, E.: Dermat. Ztschr. **62**:63-68, 1931. (*c*) Suggestion Treatment and Warts, Queries and Minor Notes, J. A. M. A. **106**:235-236 (Jan. 18) 1936.

disappearance of the warts in many instances. A wart disappeared four days after one treatment without reaction, discomfort or subsequent scar. In other cases two to eight weeks elapsed between the therapy and the cure. Even with the longer interval the result was relatively rapid.

*Summary.*—Records of treatment were available for 748 patients. Sixty-eight and seven-tenths per cent had verruca vulgaris; 21.5 per cent had verruca plantaris; 6.8 per cent had verruca plana juvenilis, and 3 per cent had verruca filiformis.

TABLE 5.—*Psychotherapy in the Treatment of Warts (Seven Cases)*

| Number | Present Age | Sex | Age at First Attack | Duration Before Treatment, Yrs. | Treatment by: Relative (R), Layman (L), Physician (P) | Duration of Treatment | Number of Treatments | Treatment Failure or Success | Means Used | Recurrence | New Attack | Free Period, Yrs. | No More Warts |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 20 | M | 16 | 5/12 | L | — | 1 | S | Cord tied around one wart; all warts gone in short time | 0 | 0 | 3½ | + |
| 2 | 30 | M | 24 | ½ | R | — | 1 | S | Tied red cotton thread around wart and buried lock of hair under stone in field; wart gone in one week | 0 | 0 | 5½ | + |
| 3 | 30 | F | 10 | ½ | L | — | 1 | S | Stole raw beef from butcher; rubbed on warts; buried meat; warts gone in one week | 0 | 0 | 20 | + |
| 4 | 39 | F | 12 | ? | L | — | 1 | S | Old man passed his hand over wart and then rubbed her head | 0 | 0 | 27 | + |
| 5 | 45 | M | 15 | ? | L | — | 1 | S | Washed hands in morning dew once; warts gone in a month | 0 | 0 | 30 | + |
| 6 | 55 | M | 14 | 2 | P (quack) | — | 1 | S | "Doctor" rubbed fingers over warts and mumbled a few words; warts gone in one week | 0 | 0 | 39 | + |
| 7 | 69 | M | 16 | ½ | L | — | 1 | S | Patient taken to harness maker by father, who said man had reputation in curing warts; harness maker knotted a cord over each wart; warts soon gone | 0 | 0 | 52 | + |

An analysis of this series reveals that: 1. In less than one fourth of the cases the records covered a period longer than one month. 2. Of 160 cases of this kind, probable cures were obtained in 88 and probable failures in 72. 3. Electrodesiccation was the treatment most frequently used for verruca vulgaris and verruca filiformis. 4. Roentgen therapy was most frequently used for plantar warts. 5. Various combinations of treatment were used for verruca plana juvenilis. 6. The

TABLE 6.—*Recurrence of Warts (Forty-One Cases)*

| Case | Type * | Duration, Years | Treatment | First Recurrence, Days | Treatment | Second Recurrence, Days | Treatment | Third Recurrence, Days |
|---|---|---|---|---|---|---|---|---|
| 1 | VV | 7/12 | Desiccation | 31 | ..... | .. | ..... | .. |
| 2 | VV | 5 | Desiccation and roentgen therapy | 42 | Same | 63 | Desiccation | 90 |
| 3 | VV | 2 | Desiccation | 28 | Same | 41 | Desiccation | 28 |
| 4 | VV | 2 | Desiccation and roentgen therapy | 161 | Desiccation | 21 | Desiccation | .. |
| 5 | VV | ¾ | Desiccation | 49 | Desiccation | .. | ..... | .. |
| 6 | VV | 2 | Roentgen therapy | 60 | Desiccation | 59 | Roentgen therapy | ? |
| 7 | VV | ¼ | Roentgen therapy | 41 | Roentgen therapy | ? | Desiccation | ? |
| 8 | VV | ? | Excision | ? | Roentgen therapy | No revisit | | |
| 9 | VV | ¼ | Desiccation | 28 | Desiccation | No revisit | | |
| 10 | VV | 1 | Desiccation | 21 | Desiccation | | | |
| 11 | VV | 2½ | Desiccation | 24 | Desiccation | 151 | ..... | .. |
| 12 | VV | 1 | Desiccation | ? | Desiccation | No revisit | | |
| 13 | VV | 3 | Combined | ? | ..... | .. | ..... | .. |
| 14 | VV | 2 | Curettage and acid | 209 | Desiccation | 53 (no revisit) | | |
| 15 | VV | 3 | Endothermy | 1 yr. | Desiccation | 21 (no revisit) | | |
| 16 | VV | 1 | Endothermy | 59 | Desiccation | No revisit | | |
| 17 | VV | ? | Endothermy | ? | Roentgen therapy | No revisit | | |
| 18 | VV | 1 | Endothermy | 37 | Desiccation | No revisit | | |
| 19 | VV | ? | Endothermy | 217 | Desiccation | Many recurrences for two years | | |
| 20 | VV | ¼ | Endothermy | 91 | Desiccation | No revisit | | |
| 21 | VV | 1/12 | Endothermy | 36 | Roentgen therapy | No revisit | | |
| 22 | VV | ⅙ | Endothermy | 125 | Desiccation | .. | ..... | .. |
| 23 | VV | ⅙ | Endothermy | 59 | Roentgen therapy | .. | ..... | .. |
| 24 | VV | ? | Excision | 31 | Roentgen therapy | .. | ..... | .. |
| 25 | VV | 2 | Excision | ? | ..... | .. | ..... | .. |
| 26 | VV | 1 | Desiccation | 60 | Combined | .. | ..... | .. |
| 27 | VV | 1 | Desiccation | ? | Desiccation | .. | ..... | .. |
| 28 | VV | 2 | "Hot needle" | ? | Later spontaneous disappearance | | | |
| 29 | VP | ? | Roentgen therapy | ? | Roentgen therapy | No revisit | | |
| 30 | VF | ½ | Desiccation | 122 | Desiccation | No revisit | | |
| 31 | VP | 1 | Excision Promptly | | Roentgen therapy | 3 yr. (?) roentgen therapy (failed) still present | | |
| 32 | VV | ? | Desiccation | 70 | Desiccation | .. | ..... | .. |
| 33 | VP | 1/12 | Excision | ? | Roentgen therapy | No revisit | | |
| 34 | VP | 5/12 | Desiccation | 231 | Roentgen therapy | No revisit | | |
| 35 | VP | 5 | Roentgen therapy | 297 | Roentgen therapy; later endothermy; then desiccation | .. | ..... | .. |
| 36 | VP | 3 wk. | Desiccation | 60 | Not recorded | No revisit | | |
| 37 | VP | 1 | Roentgen therapy | 133 | Roentgen therapy and desiccation | Not followed | | |
| 38 | VP | ¼ | Roentgen therapy | 403 | Roentgen therapy and desiccation | Not followed | | |
| 39 | VP | ? | Desiccation | 1 yr. | Roentgen therapy | No revisit | | |
| 40 | VP | 7 (?) | Excision (repeated) | ? | Radium every two weeks for past year; radiodermatitis | .. | ..... | .. |
| 41 | VP | ⅙ | Roentgen therapy by two physicians; failure; excision after 2 years | 40 | Excision | 39 | Repeated recurrences | |

* VV indicates verruca vulgaris; VP, verruca plantaris; VPJ, verruca plana juvenilis; VF, verruca filiformis.

percentage of cures obtained by any treatment or combination of treatments was not higher than 55 per cent in this group. 7. Electrodesiccation and radiation therapy were the methods of treatment most frequently used. The percentages of cures by the two methods were approximately the same.

## RECURRENCES

Warts are a minor malady. Physician and patient are likely to part company when they have disappeared. Yet recurrences take place. I am not referring to new warts or to succeeding attacks but to recurrence in situ. How commonly this happens and what interval should be allowed before cure is claimed are unknown.

In this series 41 patients were treated for recurrent warts. The free period before recurrence was known in only a few of these and averaged eighty-eight days. These patients returned for treatment on an average of four and one-half months after being discharged as cured.

Twenty-three of these patients with recurrent warts had been treated by electrodesiccation; 6 had had roentgen ray treatment; 6 had had excision; 5 had had more than one form of therapy, and 1 had been treated by a "hot needle."

Recurrences are noticed on the average about three months after apparent cure and may take place at a much later time. Therefore, claims that a given method of treatment results in a certain percentage of cures should be made only after the patients have been followed for at least six months.

## SUMMARY AND CONCLUSIONS

Verrucae are pinhead-sized to bean-sized circumscribed or confluent elevations of the skin due to epidermal and papillary hypertrophy. They have a characteristic structure, so that microscopic diagnosis is possible.

This abnormal cellular hypertrophy is due to local infection with a virus.

Whether separate viruses cause the five different forms or whether the different forms are clinical variations resulting from one virus is not known.

There are five clinical types of verrucae: verruca vulgaris, verruca plantaris, verruca plana juvenilis, verruca filiformis and verruca acuminata.

Warts are autoinoculable and transmissible.

Warts are slightly more common in females than in males.

Analysis of the reported cases suggests that certain families have a relatively higher resistance to infection with wart virus than other families.

Many warts disappear without treatment. The average duration of untreated warts is between two and three years. The shortest duration in this series was one month. The longest duration was twenty-eight years, and in this case the wart is still present.

No satisfactory explanation has been offered for the spontaneous disappearance of warts.

Antibodies are known to be produced in animals infected with warts, and, by inference, it may be assumed that antibodies are produced in man. However, antibody production in virus diseases does not explain recovery.

If wart antibodies occur in man, their production must be slow, since satellite warts sometimes appear after the primary wart has been present for years.

In theory, immunity, temporary or permanent, follows antibody production. If immunity occurs in man it is temporary.

Multiple warts are more frequent than single warts in persons applying for treatment, and the percentage of multiple warts increases with delay in seeking treatment.

Cure is more probable of single than of multiple warts.

Cure is more probable when treatment is begun relatively early.

There is no specific treatment for warts.

Because recurrences are several months in appearing, statistical studies of the treatment of warts should be limited to cases which have been followed for at least six months after apparent cure.

Further study of the virus or viruses causing warts in man is desirable.

An investigation of wart antibody production in man should be made.

147 East Fiftieth Street.

# CONTACT DERMATITIS DUE TO CODEINE

R. B. PALMER, M.D.
LINCOLN, NEB.

Eczematous dermatitis due to contact with opium and its derivatives has been recorded in the foreign literature for many years. Touraine [1] thoroughly reviewed the literature, and Touraine and Scemama [2] reported a case. Since these reports, I find no reference in the foreign literature.

In the American literature the published reports are few. Heller [3] reported a case of eczematous dermatitis from lead and opium lotion and proved that the condition was due to opium. Cummer [4] reported a case of dermatitis of the eyelids from ethylmorphine hydrochloride, the sensitivity having developed after eleven years' use of the drug. Jordon and Osborne [5] reported 4 cases of eczematous contact dermatitis from opium and its derivatives and called attention to its occupational aspects. Since the last-mentioned report, I find no references in the American literature.

## REPORT OF A CASE

Miss M. P. C., aged 20, white, was seen on Jan. 11, 1939 complaining of an eruption on the face, neck and arms. The condition was of four months' duration, first appearing in the left cubital fossa and then involving the right forearm, the eyelids and the neck. She had received fractional roentgen therapy and a variety of local treatments with little improvement.

The patient was a student nurse and had entered training sixteen months previously. Two months prior to the onset of the eruption she began service in the drug room and at the time of the onset she was in this service as well as on medical and surgical ward duty. She had noticed that the eruption was better when she arose in the morning and was most intense in the evenings. The only period of freedom from eruption had been during four weeks' absence

1. Touraine, A.: Les dermatoses de l'opium, Rev. de méd. **53**:449 (Nov.) 1936.

2. Touraine, A., and Scemama: Dermatite professionnelle par dérivés de l'opium, Bull. Soc. franç. de dermat. et syph. **43**:1694 (Nov.) 1936.

3. Heller, N. B.: Acute Dermatitis Due to Opium Preparations, Arch. Dermat. & Syph. **24**:417 (Sept.) 1931.

4. Cummer, C. L.: Dermatitis of Eyelids Caused by Dionin: Development of Local Hypersensitiveness After Eleven Years' Use, Arch. Dermat. & Syph. **23**:68 (Jan.) 1931.

5. Jordon, J. W., and Osborne, E. D.: Contact Dermatitis from Opium Derivatives, with Special Reference to Occupational Aspects, J. A. M. A. **113**: 1955 (Nov. 25) 1939.

from active nursing duty. On her return, the eruption had promptly reappeared. She had attempted some patch tests herself and stated that no substances except cough syrup had elicited any reaction.

There was no history of asthma, hay fever, hives or other previous eruptions.

There was a dermatitis of fine papular character with considerable redness and swelling involving both cubital fossae, the exposed portion of the neck and the right postauricular region. The eyelids showed slight edema, redness and scaling. On the sides and dorsum of the left middle finger was a fine vesicular dermatitis.

Contact tests (fifty-four in all) were made, with the common potted plants and flowers about a hospital ward, drugs, antiseptics, chemicals with which she had contact and the local preparations used on the skin since the eruption began. These substances were applied to the back for forty-eight hours, and the reactions were read in forty-eight and seventy-two hours. Three different mercurial preparations gave a 1 plus reaction and the cough syrup a 2 plus reaction. At this time a sojourn from active duty again resulted in remission, and the patient decided to attend the university for nine months before resuming nurses' training. Control contact tests with the cough mixture on 4 other patients with contact dermatitis gave negative results.

The ingredients [6] of the cough syrup were obtained in separate solutions and in the same dilution as occurred in the mixture. On June 5 contact tests were made with these ingredients, with codeine phosphate (1 per cent aqueous solution) and with morphine sulfate (1 per cent aqueous solution). The solutions were applied to the back for forty-eight hours, and the reactions were read in forty-eight and seventy-two hours. A 3 plus reaction (papulovesicular) was obtained with codeine and with morphine. The sites of the positive reactions showed slight redness and scaling three weeks after removal of the test substances. Control tests on myself gave entirely negative reactions.

Further contact tests made on the back in the same way elicited the following results:

| | 48 Hour Reading | 72 Hour Reading |
|---|---|---|
| 1. Morphine sulfate, 1:100 aqueous solution | 2 plus | 2 plus |
| 2. Codeine phosphate, 1:100 aqueous solution | 2 plus | 2 plus |
| 3. Ethylmorphine hydrochloride, 1:100 aqueous solution | 2 plus | 2 plus |
| 4. Diacetylmorphine, 1:100 aqueous solution | 2 plus | 2 plus |
| 5. Apomorphine hydrochloride, 1:100 aqueous solution | Plus or minus | 1 plus |
| 6. Papaverine hydrochloride, 1:100 aqueous solution | Plus or minus | Plus or minus |
| 7. Morphine sulfate, 1:1,000 aqueous solution | 2 plus | 1 plus |
| 8. Codeine phosphate, 1:1,000 aqueous solution | 2 plus | 1 plus |
| 9. Ethylmorphine hydrochloride, 1:1,000 aqueous solution | 2 plus | 1 plus |
| 10. Diacetylmorphine, 1:1,000 aqueous solution | 2 plus | 1 plus |
| 11. Apomorphine hydrochloride, 1:1,000 aqueous solution | Negative | Negative |
| 12. Papaverine hydrochloride, 1:1,000 aqueous solution | Negative | Negative |

Twelve days after removal of the test substances, the sites exposed to morphine, codeine, ethylmorphine hydrochloride and diacetylmorphine showed redness and scaling, while in the sites of the tests with apomorphine and papaverine hydrochloride no reaction was visible. With these tests no focal flare-up of the eruption was evident.

At a later date, in an attempt to find a chemical antidote, a morphine sulfate tablet, ⅛ grain (8 mg.), was powdered and applied dry to two areas on the

6. Each fluidounce (30 cc.) contains: chloroform, 2 minims (0.12 cc.); codeine phosphate, 1 grain (0.065 Gm.); potassium guaiacolsulfonate, 8 grains (0.5 Gm.); ammonium chloride, 8 grains (0.5 Gm.), and antimony and potassium tartrate, 1/12 grain (0.005 Gm.), with syrup of white pine and syrup of wild cherry.

back, and a codeine sulfate tablet, ¼ grain (16 mg.), was powdered and applied dry to two areas. The material was left on for forty-five minutes, after which compresses with 1 : 3,000 potassium permanganate solution were applied for forty-five minutes, the compresses being changed every three to five minutes. The four test sites were covered with gauze and inspected two and five days later. There was no local reaction from any of these tests, but two days after their application there was a recurrence of the eruption at the sites of former involvement, and the patient had not been around opium or its derivatives. Before further tests could be carried out, she disappeared from observation, in June 1939.

The patient now resides in a distant state, but a letter received two years later is as follows: "Since my last visit, I have had some cutaneous trouble on two occasions. The first was in January 1940. My husband had a severe attack of the flu, and the physician prescribed some medicine in tablet form. I gave him the medicine, and within eighteen hours I noticed my skin becoming red and irritated as it had done before. My eyelids, arms and fingers were again affected. On inquiry I found that the tablets contained codeine. Within a week my skin was normal again. The other occasion was in October 1940. About 11 : 00 p. m. in the evening I foolishly took some cough medicine and went to bed. About 1 : 00 a. m. I was awakened feeling very uncomfortable. My entire body was covered with welts, and I really felt ill. I do not remember how long it took before my skin cleared, but the condition lasted several days. The cough medicine contained codeine."

## COMMENT

Opium contains two chemically distinct groups of alkaloids: (1) those with an isoquinoline nucleus, of which papaverine, narcotine and narceine are examples, and (2) those with a phenanthrene nucleus, of which morphine, codeine (monomethylmorphine) and thebaine (dimethylmorphine) are natural alkaloids, from which are manufactured apomorphine hydrochloride, ethylmorphine hydrochloride and diacetylmorphine.

Jordon and Osborne [5] stated that in most of the cases of contact dermatitis due to opium compounds the offending drugs have been the phenanthrene derivatives. Touraine and Scemama [2] reported a case in which the isoquinoline derivative, papaverine, seemed to be the main offender. In my case the phenanthrene derivatives (morphine, codeine, ethylmorphine hydrochloride and diacetylmorphine) seemed to be the responsible allergens.

Since chemical antidotes have been reported [7] as useful in the prevention of contact dermatitis from certain chemicals, and since Sollmann [8]

7. Obermayer, M. E.: Eczema Due to Hypersensitiveness to Rubber, Arch. Dermat. & Syph. **27**:25 (Jan.) 1933. Foerster, O. H.: Match and Match Box Dermatitis, J. A. M. A. **81**:1186 (Oct. 6) 1923. Helmke, R.: Ueber Versuche, die Entstehung der Primeldermatitis zu verhindern, Dermat. Wchnschr. **105**:1257 (Sept. 25) 1937; Ueber die Verhinderung der Primeldermatitis durch Ammoniak, ibid. **106**:669 (June 11) 1938.

8. Sollmann, T.: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 288.

mentioned potassium permanganate as a chemical antidote for morphine poisoning due to ingestion, tests were made to see if it might be useful in the prevention or amelioration of symptoms. Although potassium permanganate might not be of practical value because of its staining qualities, had it proved successful, tests with other oxidizing agents were contemplated. Because the powdered forms of codeine and morphine were used, the value of potassium permanganate in contact dermatitis from these drugs was not determined.

In cases of contact tests with other chemicals, the powdered form of the chemical has elicited positive reactions, and Sulzberger and Rostenberg [9] listed a number of chemicals in powder form as being satisfactory for contact testing. In this case, patch tests with codeine and morphine in dilutions of 1 : 100 and 1 : 1,000 gave definite local reactions without causing an exacerbation of the existing eruption, but tests with the pure powder gave negative local reactions yet caused a definite recurrence of the eruption. Although reactions to patch tests are rarely positive in cases of dermatitis medicamentosa, Scheer and Keil [10] reported a case of scarlatiniform exanthem from ingestion of codeine in which a contact test with a solution of codeine gave a positive reaction and a similar test with the powder gave a negative reaction.

Allergens which produce contact eczematous dermatitis may arrive at the skin and produce similar reactions not only by external contact but also by ingestion or injection, provided the skin is sufficiently sensitive and enough of the allergen reaches the shock tissue. In the case of Heller,[3] an eczematous dermatitis due to a lotion containing opium recurred from ingestion of a cough medicine containing opium. In a case reported by Jordon and Osborne [5] codeine given orally had caused a generalized exanthem (type of eruption was not stated), and since then external contact had caused an eczematous eruption. In my case, while I did not observe the recurrences personally, it seems that the recurrence following external contact was identical with the previous eruption and affected the previously involved areas, while the recurrence following ingestion was of a different, i. e. urticarial, type.

Considering the many people in contact with opium and its derivatives, eczematous sensitivity to this drug must be of relatively infrequent occurrence; however, in cases of contact dermatitis among nurses, doctors and pharmacists in which the allergen is not readily discovered, opium and its derivatives deserve consideration.

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9. Sulzberger, M. B., and Rostenberg, A.: A List of Substances for Patch Testing and the Concentrations to Be Employed, J. Invest. Dermat. **2**:93 (June) 1939.

10. Scheer, M., and Keil, H.: Skin Eruptions of Codeine, J. A. M. A. **102**:908 (March 24) 1934.

SUMMARY

A case of contact eczematous dermatitis due to codeine is reported and discussed.

Contact tests with powdered morphine and codeine gave negative results; those with aqueous solution (1 : 100 and 1 : 1,000) of morphine, codeine, ethylmorphine hydrochloride and diacetylmorphine elicited positive reactions. The patient reported that subsequent contact with coedine caused a recurrence and subsequent ingestion of the drug caused an eruption.

1016 Sharp Building.

# WELTMANN'S SERUM COAGULATION REACTION IN CASES OF DERMATOSES AND OF SYPHILIS

KARL STEINER, M.D.
NEW YORK

Weltmann [1] found that when normal serum is heated in a boiling water bath, coagulation occurs after a few minutes, and diffuse turbidity develops. If, however, the serum has been diluted 1 : 50 with distilled water, coagulation takes place only if certain electrolyte solutions are added. Then flocculation, as well as turbidity, occurs. Within a certain range the intensity of this coagulation is directly proportional to the nature and concentration of the electrolyte.[2]

Weltmann [1] found also that when normal serum is diluted 1 : 50 with differently concentrated solutions of calcium chloride in distilled water, different intensities of turbidity and flocculation occur after fifteen minutes of heating. He also demonstrated that the concentrations of calcium chloride at which turbidity and flocculation first appear are constant, provided normal serums have been used. Since a beginning flocculation may be distinguished more easily than a slight turbidity, only the flocculation values are considered in estimating the results of the test. The normal threshold of flocculation lies at a concentration of from 0.04 to 0.05 per cent of calcium chloride; turbidity is present at a concentration of from 0.01 to 0.02 per cent lower.

Weltmann [1] was also the first to use the coagulation reaction test on pathologic serums, and from the beginning its clinical usefulness was evident. It has been found that many diseases change the serum coagulation in a definite and characteristic manner. In certain pathologic states the serum coagulates at concentrations as low as from 0.01 to 0.03 per cent, and in others only at from 0.06 to 0.1 per cent.

Since the test is performed with ten test tubes of decreasing concentrations (from 0.1 to 0.01 per cent), the result is represented by a "band" of tubes in which flocculation has occurred. The coagulation

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. Weltmann, O.: Ueber die Spiegelung exsudativ-entzündlicher und fibröser Vorgänge im Blutserum, Med. Klin. **26**:240-245 (Feb. 14) 1930.

2. Kretz, J., and Kudlac, O.: Untersuchungen über das Verhalten der Serum-Eiweisskörper mittels der Weltmannschen Reaktion, Ztschr. f. klin. Med. **127**: 590-608, 1934.

band, corresponding to the threshold concentration, is either longer or shorter than normal—prolonged or shortened. The normal coagulation band comprises seven or six test tubes, corresponding to the threshold concentrations of 0.04 and 0.05 per cent. A prolonged coagulation band includes more than seven tubes, corresponding to concentrations lower than 0.04 per cent. Accordingly, a shortened coagulation band consists of fewer than six tubes, corresponding to concentrations higher than 0.05 per cent. Since the higher concentrations are on the left side of the series of test tubes and the lower ones on the right side, a shortened coagulation band is called a "shift to the left" and a prolonged band a "shift to the right." These terms have been chosen to correspond, more or less correctly, to the expressions used in the characterization of blood pictures. On account of the nature of the diseases which he first investigated Weltmann found more often a shift to the right. To distinguish more exactly between normal and pathologic coagulation bands he therefore used also the concentration of 0.035 per cent and considered a flocculation at that concentration to be pathologic. This eleventh tube has also been used by most of the recent investigators.

Weltmann [1] and his collaborators found also characteristic changes in some special groups of diseases. Subsequently these results were confirmed and new ones added by Weltmann and many other investigators, as reported in more than one hundred papers. The most important of these observations was the usually regular occurrence of shortened coagulation bands in exudative conditions (e. g., lobar pneumonia, ulcerative pulmonary tuberculosis and acute rheumatic fever) and of prolonged coagulation bands in fibrotic conditions (e. g., cirrhosis, hepatitis, chronic nephritis and hemolytic icterus). On the whole, the coagulation reaction test was proved to be of limited but reliable value for the differential diagnosis and prognosis of many medical diseases and of surgical, gynecologic, pediatric and other conditions.

In spite of the theoretic knowledge and the wealth of experimental and clinical information which has been obtained, the basis of the coagulation reaction test is not yet completely understood. It is apparent that the reaction is not of an immunologic character (of the antigen-antibody type). It is therefore nonspecific, like the erythrocyte sedimentation rate or leukocytosis, to both of which it has been compared. The most important chemical fact which has emerged from the numerous experiments performed with the coagulation reaction test is that the coagulated substance is protein. Consistent with this fact are the changes observed in the reaction by the addition or removal of protein, by a greater or lesser protein content, by hemolysis, probably also by an inverse albumin-globulin ratio and, particularly significant, by a qualitative alteration of the serum protein. The protein nature of the reaction is also confirmed

by its colloidal character. Adsorption on kaolin and injection of acacia change the outcome of the test. The addition of lipids to the reaction system or a variation in the lipid content of the serum also affects the results, probably by the action of lipids on calcium. Physical factors, such as irradiation, freezing and inactivation have no effect on the reaction. Various chemical substances (bile, amino acids and nonprotein nitrogen) have been found of no significance. The $p_H$ of the serum appears to be of no importance. Recent surveys of all these details and of all clinical results are contained in the papers of Dees [3] and Rosegger.[4]

## TECHNIC

The following technic was used almost exactly in accordance with the original method of Weltmann.

A 5 per cent stock solution of calcium chloride ($CaCl_26H_2O$) in distilled water was prepared. It is apparent that the coagulation reaction must be affected by the amount of water of crystallization in the salt. This observation has been reported also by several investigators. In a few of my own experiments with dehydrated calcium chloride the coagulation band was found to be 0.01 per cent to 0.025 per cent longer than that in the controls. This was to be expected because of the higher concentration of the dehydrated saline solution. Certain small discrepancies in the reports of a few investigators may be attributed to this fact. To account for the variable water of crystallization, the solution was tested as to its specific weight and was constantly kept at a specific gravity of 1.040 (Kretz and Kudlac [2]).

This stock solution and all other solutions are best kept in glass-stoppered flasks or small bottles with tightly fitting stoppers and a wide neck, so that large pipets may be easily introduced. All vessels, pipets, test tubes, measuring glasses and funnels should be carefully washed with distilled water before they are used. The ten dilutions of 0.1 to 0.01 per cent and a dilution of 0.035 per cent were made freshly with distilled water from the stock solution at about weekly intervals.

From 3 to 5 cc. of blood was taken from the patient and left standing in the refrigerator for from twelve to twenty-four hours. Aging of the serum for one to two days had no effect on the outcome of the coagulation reaction (Balan [5]). The blood was centrifuged for from ten to fifteen minutes. Serums that showed

3. Dees, S. C.: A Clinical Study of the Weltmann Serum Coagulation Reaction, J. Pediat. **17**:44-52 (July) 1940; An Experimental Study of the Weltmann Serum Coagulation Reaction, ibid. **17**:53-72 (July) 1940; The Value of the Weltmann Serum Coagulation Reaction in Allergic Disease, South. M. J. **34**: 586-592 (June) 1941.

4. Rosegger, H.: Klinische Erfahrungen mit dem Weltmannschen Koagulationsband, Ztschr. f. klin. Med. **135**:495-532, 1939; Experimentelle Beeinflussbarkeit des Weltmannschen Koagulationsbandes, ibid. **135**:441-453, 1939; Das Weltmannsche Hitzekoagulationsband, Ergebn. d. inn. Med. u. Kinderh. **57**:183-240, 1939.

5. Balan, E.: Das Koagulationsband von Weltmann bei Syphilis, Arch. f. Dermat. u. Syph. **173**:483-494, 1936.

hemolysis were discarded. Kaiser [6] and others found the coagulation bands with hemolyzed serums to be from 0.01 to 0.02 per cent prolonged. My own controls gave similar results. This is due probably to the higher protein content of hemolyzed serum. In contrast to hemolysis, an increased lipid content (grossly visible) does not change the flocculation threshold, as my own tests showed.

After the serum had been centrifuged, 5 cc. of each solution of calcium chloride was measured into eleven test tubes. To each dilution was added 0.1 cc. of the serum by pipet. The content of each tube was thoroughly mixed by tilting. Then the rack with the tubes was immersed in the boiling water bath.

After fifteen minutes the rack was removed and the flocculation threshold noted. In the examination of the coagulation band a slight flocculum at the bottom of a test tube should never be considered as the result. The real flocculation threshold is indicated by some flocculation, no matter how little, suspended in the fluid. This mode of judging the results conforms to Weltmann's procedure. It is possible that differences in the results of some investigators may be due in part to such a mistake. The sediment at the bottom appears frequently one test tube lower than the suspended flocculation.

## RESULTS

The coagulation reaction test was performed on the serums of 409 patients. In addition, 257 serums from many of the same patients served for repeated examinations up to 6 times. The total number of all tests performed was therefore 666.

Five hundred and eighteen of the serums originated from 337 patients with dermatoses. Of these 518 serums 181 were used for repeated tests. One hundred and forty-eight serums had been taken from 72 syphilitic patients. Therefore 76 of these 148 serums were tested in repeated examinations.

The results of the coagulation reaction tests in patients with dermatoses are listed in table 1. Only 106 of the 518 serums gave a normal coagulation band of 0.04 or 0.05 per cent. Still fewer serums (29) showed a shift to the left, while with a great majority (383) the coagulation band was prolonged, in many cases at least to 0.035 per cent, in most cases to 0.03 per cent and in a few cases even to 0.02 per cent. These figures correspond to about 20 per cent normal, 74 per cent prolonged and 6 per cent shortened coagulation bands. It may be assumed, therefore, that cutaneous diseases in general tend to cause a moderate but distinct prolongation of the coagulation band.

Eczematous eruptions were present in about 60 cases, including seborrheic dermatitis, dermatitis venenata, atopic dermatitis and circumscribed neurodermatitis. No particularly characteristic coagulation bands were found. However, it seems remarkable that in none of these cases was there a shortened band. In the great majority of instances the

6. Kaiser, T.: Beiträge zur Weltmannschen Serumkoagulation bei Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **83**:271-279, 1933.

coagulation band was moderately prolonged, to 0.035 per cent, as far as 0.03 per cent and in a few isolated cases to 0.02 per cent. It was the definite impression that the shift to the right was more frequent and stronger in cases in which a larger area was affected and in which the inflammation was more severe.

Fungous diseases, including dermatophytosis and dermatophytids of the hands and feet, tinea corporis, pityriasis versicolor and sycosis mycotica, were present in about 60 cases. As in the cases of eczema, no typical coagulation bands were found. A higher frequency of the prolonged bands was again noted.

There were 40 cases of psoriasis vulgaris, in 7 of which the condition was complicated by other diseases. In the remaining 33 cases about

TABLE 1.—*Results of the Coagulation Reaction Test in Dermatoses*

| | | | | Normal Range | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Per cent..... | 0.02 | 0.03 | 0.035 | 0.04 | 0.05 | 0.06 | 0.07 | 0.08 | Total |
| First coagulation band..... | 3 | 142 | 99 | 46 | 32 | 7 | 7 | 1 | 337 |
| Repeated coagulation bands. | 8 | 87 | 44 | 13 | 15 | 9 | 5 | .. | 181 |
| All coagulation bands..... | 11 | 229 | 143 | 59 | 47 | 16 | 12 | 1 | 518 |

TABLE 2.—*Results of the Coagulation Reaction Test in Psoriasis*

| | | | | Normal Range | | |
|---|---|---|---|---|---|---|
| Per cent..... | 0.02 | 0.03 | 0.035 | 0.04 | 0.05 | Total |
| First coagulation band..... | .. | 19 | 11 | 2 | 1 | 33 |
| Repeated coagulation bands..... | 1 | 27 | 3 | 2 | .. | 33 |
| All coagulation bands..... | 1 | 46 | 14 | 4 | 1 | 66 |

the same results were obtained as in the cases of eczematous and fungous conditions. Since the cases of psoriasis, in contrast to those of eczema and fungous conditions, represented a highly homogeneous group, their coagulation reactions may be regarded as the prototype of the average behavior of the reaction in cutaneous disease in general. For that reason, a detailed account of the coagulation band in psoriasis is given in table 2.

A prevalence of the prolonged coagulation bands (61 out of 65) and a complete absence of shifts to the left are demonstrated here. The frequency and the extent of the shift to the right surpass considerably even those of the two aforementioned groups. This peculiarity is due perhaps to the fact that in the case of many of the patients with psoriasis large areas of the skin were affected, while in the other groups there was also a considerable number of minor conditions. The 7 cases of psoriasis with complications are listed in table 3.

It will be noted that a typical coagulation band becomes changed when it is "superimposed" by a different coagulation band of another disease. The exudative processes of pulmonary tuberculosis prevailed over the psoriatic type by producing shortened coagulation bands. Progressive improvement of the pulmonary tuberculosis expressed itself in increasing flocculation thresholds of successive coagulation bands. Unexpectedly atypical coagulation bands should therefore always be regarded as cause for a more careful examination of the patient.

In addition to the cases of eczema, dermatophytosis and psoriasis the serums examined originated from more than 50 cases of the following cutaneous diseases: staphylodermas, impetigo, pityriasis rosea, acne, rosacea, erythema (medicamentosum, nodosum, multiforme), urticaria, pruritus, herpes simplex and zoster, lichen planus, basal and prickle cell epitheliomas, nevi and pigmentations, hyperkeratoses, idiopathic atrophy, erythrodermas (essential and secondary), tuberculosis of the skin, lupus

TABLE 3.—*Results of the Coagulation Reaction Test in Psoriasis with Complications*

| Complications | Coagulation Reaction | | | |
|---|---|---|---|---|
| | First | Second | Third | Fourth |
| Acne rosacea | 0.035 | 0.04 | 0.03 | ..... |
| Gallstones | 0.03 | .... | .... | ..... |
| Obesity | 0.03 | .... | .... | ..... |
| Cancer | 0.04 | .... | .... | ..... |
| Indurative pulmonary tuberculosis | 0.04 | .... | .... | ..... |
| Exudative pulmonary tuberculosis | 0.07 | 0.07 | 0.035 | 0.035 |
| Exudative pulmonary tuberculosis | 0.07 | 0.06 | 0.05 | ..... |

erythematosus, ulcus cruris, burns, frost bites, scabies, pediculosis and alopecias.

In general, all these diseases gave 0.01 to 0.02 per cent prolonged coagulation bands. This result might be expected, as it is consistent with the aforementioned figures. With all these diseases there were also patients with normal findings, provided several patients had been examined. The shift to the right was perhaps accentuated in patients with epitheliomas, while severe burns and, to a greater extent, diffuse erythrodermas caused a relative or even absolute shift to the left.

Except for 16 cases of varicose ulcers of the legs, all these diseases were represented by only a few cases (up to 11). These small numbers do not permit a definitive evaluation of the coagulation bands. Perhaps in certain instances, as in erythrodermas, burns and epitheliomas, a greater number of cases would reveal more characteristic coagulation reactions.

In relatively few cases the coagulation bands were distinctly shortened or greatly prolonged. In most of these the disease was superimposed by complications, such as tonsillitis, pulmonary tuberculosis, cirrhosis and status febrilis.

Only two diseases were characterized by coagulation bands of such unusual quality and regularity that it seems justified to rely on these figures, although the number of the tests performed was small. Table 4 gives the results of the coagulation reaction tests in these two diseases, pemphigus and sclerodrema (diffuse acrosclerosis).

On first examination the serums of 3 patients with pemphigus showed shifts to the left greater than that of any other uncomplicated cutaneous disease. The same coagulation bands were obtained with bullous fluid. The disease of the fourth patient, whose serum gave a prolonged coagulation band, was of atypical nature. It began as chronic pyoderma of the scalp and persisted for a long time at that stage. This fact may account for the atypical coagulation reaction in comparison with those of the other 3 patients. In any case, the peculiarity of the coagulation band in pemphigus cannot be denied. In this connection it is interesting to note that 4 patients with dermatitis herpetiformis did not show

TABLE 4.—*Results of the Coagulation Reaction Test in Pemphigus and Scleroderma*

| | Coagulation Reaction | | | | | | |
|---|---|---|---|---|---|---|---|
| | First | Second | Third | Fourth | Fifth | Sixth | Seventh |
| Pemphigus..... | 0.07 | 0.06 | 0.06 | 0.05 | 0.08 | ..... | ..... |
| Pemphigus..... | 0.06 | 0.07 | 0.06 | 0.07 | 0.04 | 0.035 | 0.035 |
| Pemphigus..... | 0.06 | .... | .... | .... | .... | ..... | ..... |
| Pemphigus..... | 0.03 | 0.03 | 0.03 | 0.035 | 0.035 | 0.035 | ..... |
| Scleroderma..... | 0.02 | 0.02 | 0.03 | 0.03 | .... | ..... | ..... |
| Scleroderma..... | 0.02 | .... | .... | .... | .... | ..... | ..... |

unusual shifts to the left but had rather uncharacteristic reactions. Further studies might answer the question as to whether the coagulation reaction may serve as an aid in the differential diagnosis of these two diseases.

In scleroderma unusually prolonged coagulation bands were found (table 4). Although only 2 cases were available, several circumstances permit one to assume the general validity of the results obtained.

Tables 1, 2 and 4 present the results of the repeated coagulation reaction tests in summarized form. A detailed picture of the most frequently repeated and typical reactions is given in table 5. Analysis of this table offers two more facts which are of general interest. The results of the coagulation reaction tests in constitutional conditions (e. g., psoriasis) and in those chronic diseases which do not change over long periods (e. g., lupus vulgaris and scleroderma) remain almost absolutely constant. The differences in the flocculation thresholds amount to not more than 0.01 per cent. This means that the serum factors responsible for the outcome of the coagulation reaction remain unchanged and that therefore a high reliability may be adjudged to the test. The second

striking fact seen in table 5 pertains to the prognostic value of the coagulation reaction. In this regard the last 3 cases—burn and pemphigus—are interesting. The patient with the burn showed immediately after the accident a somewhat prolonged coagulation band (0.03 per cent). When exudation and toxic symptoms increased, it became shortened (to 0.05 per cent) and then returned gradually to more normal values and even again became prolonged by progressive recovery. One of the 2 patients with pemphigus showed, after an initial shift to the left

TABLE 5.—*Results of Repeated Coagulation Reaction Tests and Typical Coagulation Bands*

| | Coagulation Bands | | | | | | |
|---|---|---|---|---|---|---|---|
| | First | Second | Third | Fourth | Fifth | Sixth | Seventh |
| Lupus vulgaris | 0.04 | 0.03 | 0.035 | 0.035 | .... | ..... | ..... |
| Erythema induratum | 0.03 | 0.03 | 0.03 | 0.03 | .... | ..... | ..... |
| Erythema induratum | 0.035 | 0.03 | 0.03 | 0.035 | .... | ..... | ..... |
| Scleroderma | 0.02 | 0.02 | 0.03 | 0.03 | .... | ..... | ..... |
| Chronic staphyloderma | 0.035 | 0.035 | 0.035 | 0.03 | .... | ..... | ..... |
| Erythroderma | 0.06 | 0.05 | 0.05 | 0.06 | .... | ..... | ..... |
| Psoriasis | 0.03 | 0.04 | 0.04 | 0.03 | .... | ..... | ..... |
| Psoriasis | 0.035 | 0.03 | 0.035 | 0.03 | .... | ..... | ..... |
| Psoriasis | 0.03 | 0.03 | 0.03 | 0.03 | .... | ..... | ..... |
| Psoriasis | 0.03 | 0.03 | 0.03 | 0.03 | .... | ..... | ..... |
| Burn | 0.03 | 0.05 | 0.04 | 0.035 | .... | ..... | ..... |
| Pemphigus | 0.07 | 0.06 | 0.06 | 0.05 | 0.08 | ..... | ..... |
| Pemphigus | 0.06 | 0.07 | 0.06 | 0.07 | 0.04 | 0.035 | 0.035 |

TABLE 6.—*Results of the Coagulation Reaction Test in Syphilis*

| | | | | Normal Range | | | | |
|---|---|---|---|---|---|---|---|---|
| Per cent | 0.02 | 0.03 | 0.035 | 0.04 | 0.05 | 0.06 | 0.07 | Total |
| First coagulation band | .. | 34 | 22 | 12 | 3 | .. | 1 | 72 |
| Repeated coagulation bands | 1 | 41 | 23 | 7 | 4 | .. | .. | 76 |
| All coagulation bands | 1 | 75 | 45 | 19 | 7 | .. | 1 | 148 |

(0.07 per cent) and a subsequent prolonged tendency to normalcy, a sudden and extreme shift to the left (0.08 per cent); whereas the other showed, after repeatedly shortened coagulation bands (0.06 and 0.07 per cent), a decisive turn to normal and slightly prolonged coagulation bands (0.04, 0.035 per cent). The clinical course of these 2 patients followed closely the results of the coagulation reactions. The first patient died shortly after the last test; the second patient entered a stage of almost complete remission. These few examples indicate a prognostic value of the coagulation reaction.

All observations so far reported pertain only to cutaneous diseases. Table 6 shows the results of the test in syphilitic patients.

In syphilis, as in the dermatoses, the number of the prolonged coagulation bands was much higher than that of the normal ones (121 to 26). Only 1 of 148 tests gave a shortened coagulation band, and this was superimposed, since the patient suffered from tonsillitis. Thus the prevalence of the shift to the right (81 per cent) was even more pronounced in syphilis than in cutaneous diseases (74 per cent).

In table 7 the coagulation reactions are differentiated to correspond to the various stages of syphilis. However, no particular characteristics of the various manifestations are noticeable. A greater number of cases might provide more conclusive results. Repeated examinations of the same cases again showed high constancy of the results. No relation was present between the coagulation reaction and the Wassermann reaction.

There was only one point of special interest among the coagulation bands of syphilitic patients. In successive tests in a case of dermatitis

TABLE 7.—*Results of the Coagulation Reaction Test in Various Stages of Syphilis*

| | | | | Normal Range | | | | |
|---|---|---|---|---|---|---|---|---|
| Per cent | 0.02 | 0.03 | 0.035 | 0.04 | 0.05 | 0.06 | 0.07 | Total |
| Primary and early secondary | 1 | 17 | 13 | 5 | 1 | .. | .. | 37 |
| Tertiary | .. | 4 | 3 | 2 | 1 | .. | .. | 10 |
| Nervous | .. | 10 | 11 | 3 | 3 | .. | .. | 27 |
| Latent | .. | 41 | 17 | 7 | 2 | .. | 1 | 68 |
| Congenital | .. | 3 | 1 | 2 | 1 | .. | .. | 6 |

due to neoarsphenamine the following coagulation bands were obtained: 0.04 per cent, 0.035 per cent, 0.02 per cent, 0.03 per cent and 0.035 per cent. These corresponded to the clinical course of the dermatitis. The extreme prolongations corresponded to the spread of the condition, and the reversal to the healing of the process. In 2 other cases of dermatitis due to neoarsphenamine there was neither an extreme shift to the right nor a particular parallelism between the coagulation reaction and the clinical condition. Hepatic damage was responsible perhaps for the behavior of the coagulation band in the first case. Impaired hepatic function had been revealed by a galactose test.

## LITERATURE

In 1934 Midana and Leone [7] published a report on the coagulation bands in 51 cases of cutaneous diseases and in 20 cases of syphilis. In 18 cases of psoriasis and in 1 case of dermatitis herpetiformis there were normal or prolonged coagulation bands. Of 8 cases of leprosy, in 1 there was a shift to the left and in another a shift to the right. In

7. Midana, A., and Leone, R.: La reazione di Weltmann in dermatologia, Dermosifilografo **9**:494-503 (Sept.) 1934.

lupus vulgaris (1 case), urticaria (1 case) and erythema multiforme (2 cases) the coagulation bands were normal. In a case of mycosis fungoides the coagulation band was shortened to 0.09 per cent. These results are, on the whole, in accord with the figures presented here. In eczema, however, and in syphilis Midana and Leone obtained results somewhat different from those reported in this paper. Among 18 cases of eczema there were shortened bands in 9. In no case of eczema was a prolonged band demonstrated. In contrast to the aforementioned result in dermatitis herpetiformis, in a second case of that disease there was a shortened coagulation band. In 17 cases of early secondary syphilis there were shortened coagulation bands in 9, whereas in 3 cases of late syphilis there were normal or prolonged bands. In 2 cases of eczema, 3 cases of psoriasis and 1 case of early syphilis Midana and Leone repeated the tests after treatment had been given. The results of these were normal. This is consistent with the findings represented in tables 1, 2, 5 and 6. In general, Midana and Leone obtained somewhat shorter coagulation bands than those listed in this paper. No fundamental discrepancies, however, were to be noted as far as psoriasis, a few other dermatoses and tertiary syphilis were concerned. The insignificant differences in these instances may be explained by a slightly different technic. Perhaps the stock solutions were not quite the same. There is no explanation, however, for the divergence between the results in eczema and in early syphilis.

Two more papers on syphilis were published, one by Sicher and Wiedmann [8] and the other by Balan.[5] Each deals with 103 cases. The results are in almost complete accord with the figures in tables 6 and 7. Balan reported a few shortened coagulation bands in early syphilis. Pellegrini and Barsini,[9] however, obtained in primary syphilis prolonged bands. Longo [10] observed unusually prolonged bands in neurosyphilis. Kretz and Kudlac [2] and Teufl [11] also mentioned prolongations of the band in this disease.

Gantenberg and Rosegger [12] obtained a prolonged coagulation band (to 0.03 per cent) in a case of scleroderma and a normal one (0.04 per

8. Sicher, G., and Wiedmann, A.: Das Koagulationsband von Weltmann bei Syphilis, Med. Klin. **30**:1664-1666 (Dec. 14) 1934.

9. Pellegrini, M., and Barsini, G.: Il comportamento ed il significato delle sieroreazione di Weltmann in alcuni stati morbosi. Ricerche sul comportamento della soglia elettrolitica della coagulo-flocculazione al calore degli essudati, transudati e del liquido cefalo-rachidiano normale e patologico, Minerva med. **1**:154-162 (Feb. 3) 1934.

10. Longo, N.: La siero-reazione di Weltmann delle malattie nervose e mentali. Boll. Soc. med.-chir. Catania **2**:827, 1934.

11. Teufl, R.: Der diagnostische Wert der Serumkoagulation nach Weltmann, Wien. Arch. f. inn. Med. **29**:37 and 297, 1936.

12. Gantenberg, R., and Rosegger, H.: Bemerkenswerte Befunde bei Sklerodermie, Med. Welt **11**:597-601 (May 1) 1937.

cent) in another case. Teufl [11] obtained shortened bands in cases of burns. Monacelli [13] did not observe any alterations of the coagulation band in 18 cases of cutaneous leishmaniasis (in contrast to cases of internal leishmaniasis, in which the bands were abnormal). Ishizuka [14] examined 130 cases of venereal lymphogranuloma and found shortened bands in the initial stage, later normal bands, still later shifts to the right and by progressive recovery again reversal to normal.

COMMENT

The results reported in the literature confirm the conclusions drawn from the findings presented here. Generally, the coagulation bands in cases of cutaneous diseases and syphilis tend toward moderate but distinct prolongation. In most instances, however, they are uncharacteristic. Apparently more pronounced alterations of the reaction occur when larger areas of skin are affected and in cases of more severe diseases, as confirmed by the definitely characteristic results in pemphigus and scleroderma. The results in these diseases, however, are by no means specific. They are the expression of extreme conditions and illustrate most clearly the behavior of the coagulation reaction. The main characteristic of pemphigus is excessive bullous exudation and that of scleroderma equally excessive fibrosis. Exudation and fibrosis have been found to be decisive for the outcome of the coagulation reaction in medical and other diseases, and they appear also of the utmost importance for this reaction in diseases of the skin and in syphilis. The coagulation band is not characteristic for disease entities but for pathologic conditions. There are, of course, diseases with more constant pathologic changes which correspondingly show more characteristic coagulation bands. However, this does not mean a disease specificity. It is a group reaction occurring in a special case.

Since the coagulation reaction is variable only in two opposite directions its alterations may indicate only two opposite conditions, namely, exudation and fibrosis. Gradual differences of the reaction are characteristic for the degree to which these conditions are developed.

The last-mentioned circumstance particularly explains the usually moderate degree of the shifts of the coagulation bands in cases of cutaneous diseases. Many diseases of the skin are but slightly exudative, and only a few are very fibrotic. Almost equally important is the extent of the involvement. Extreme shifts are therefore unlikely. It is easily

13. Monacelli, M.: Recerche su la protidemia, l'equilibrio proteico e la siero-coagulazione al calore nella leishmaniosi cutanea, Gior. ital. di dermat. e sif. **78**: 1079-1091 (Dec.) 1937.

14. Ishizuka, T.: Ueber das Koagulationsband nach Weltmann bei Lymphogranulomatosis inguinalis, Jap. J. Dermat. & Urol. **43**:126 (May 20) 1938.

understandable that a few small patches of a certain disease cannot disturb the cutaneous function to such a degree that significant changes in the chemical reactions of the blood would result.

It is obvious that the problem of the chemical nature of the coagulation reaction cannot be approached on the basis of the results presented in this paper. Merely as a confirmation of facts already known it might be mentioned that certain results reported in the dermatologic literature have shown abnormal changes of the serum calcium level and of the protein content and albumin-globulin ratio in some cases of cutaneous conditions in which a shifted coagulation band was found. Nathan and Stern [15] reported increased serum calcium values in cases of non-exudative dermatoses. Talbott, Lever and Consolazio [16] found the calcium level of the serum in 10 cases of acute pemphigus reduced to less than 4 milliequivalents per liter (normal range 4.5 to 5.5 milliequivalents per liter). A hyperproteinemia and an inverse albumin-globulin ratio were also present in these cases. In scleroderma also changed serum calcium values have been mentioned.[17]

All these observations, however, do not permit a chemical interpretation of the coagulation reaction. They merely point to a disturbance in the relation between the colloids and electrolytes of the serum. In the individual case a great many pathologic conditions are bound to effect such a disturbance. Careful examination of the patients and exact measurements of the serum constituents would seem to be necessary, therefore, before the chemical interpretation of the coagulation band may be attempted.

## SUMMARY

The nature of Weltmann's serum coagulation reaction and the terms pertaining to it are explained, with brief references to the literature.

The technic of the reaction is described.

The results of the coagulation reaction tests performed on 518 serums from 337 patients with dermatoses revealed a tendency toward moderate but distinct prolongation of the coagulation bands. However, for most diseases the bands were found to be uncharacteristic. There were also

15. Nathan, E., and Stern, F.: Ueber Kalium- und Calciumschwankungen im Blutserum bei Dermatosen, Arch. f. Dermat. u. Syph. **156**:446-464, 1928.

16. (*a*) Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies in Patients with Pemphigus, J. Invest. Dermat. **3**:31-68 (Feb.) 1940. (*b*) Lever, W. F., and Talbott, J. H.: Action of Dihydrotachysterol in Chronic Pemphigus, Arch. Dermat. & Syph. **43**:341-356 (Feb.) 1941. (*c*) Talbott, J. H., and Coombs, F. S.: Pemphigus: Experimental Studies on Thirty-Four Patients, ibid. **41**:359-369 (Feb.) 1940.

17. Petersen, F. W., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, Arch. Path. **9**: 151-444 (Jan., pt. 2) 1930. Talbott, Lever and Consolazio.[16a]

cases of all conditions in which normal results were obtained. Generally speaking, the results were normal when only small areas were involved.

Definite results were obtained in pemphigus and sometimes in scleroderma (diffuse acrosclerosis). The coagulation bands in pemphigus were shortened. In scleroderma unusual prolongation occurred.

Extreme results of the coagulation test in dermatoses and in syphilis with normally uncharacteristic bands were obtained when another disease was "superimposed" on the cutaneous process.

Repeated tests performed on the serums of the same patients showed a high reliability and a certain prognostic value of the test.

The prevalence of the prolonged coagulation bands in 148 serums of 72 patients with syphilis was even more apparent than in cases of dermatoses.

In general, the results of the coagulation reaction test in cases of dermatoses and of syphilis reported in this paper are consistent with those reported in the literature.

In dermatoses, as well as in other diseases, exudation and/or fibrosis are recognized as decisive factors in the coagulation reaction. The reactions are characteristic for these pathologic states but not specific for certain diseases. In general, exudative processes produce shortened coagulation bands, and fibrotic processes produce prolonged bands. This is typically shown in the cases of pemphigus and scleroderma.

According to results reported in the literature, there appears to be a certain parallelism between the outcome of the coagulation test and the calcium level and protein content of the serum in certain cases. However, no chemical interpretation of the coagulation reaction should be attempted either in regard to results reported in the literature or on the basis of those reported in this paper.

35 Fort Washington Avenue.

# XCIX. HISTOPATHOLOGY OF THE SKIN IN PELLAGRA

ROBERT A. MOORE, M.D.
ST. LOUIS
TOM D. SPIES, M.D.
BIRMINGHAM, ALA.
AND
ZOLA K. COOPER, PH.D.
ST. LOUIS

During the past decade numerous clinical and experimental studies on pellagra have resulted in a distinct clarification of the concepts of the etiology of the disease. However, histologic studies of cutaneous lesions in human beings have not kept pace with the other advances. This may be due to the fact that the earlier studies in this field gave accurate descriptions of the acute lesions of the skin, which were accepted by most investigators. Since it has become more and more evident, however, that pellagra is a systemic disease, it would seem that additional information concerning the cutaneous manifestations might be obtained from a histologic study not only of the active lesions but also of clinically unaffected areas of skin in the same patients. The present investigation was undertaken to determine whether or not the clinically unaffected skin of patients presenting pellagrous lesions shows any deviations from the normal.

## REVIEW OF THE LITERATURE

Since most of the histologic studies of the lesions of pellagra have been incidental to clinical studies and case reports, only a few of the more important articles are reviewed here.

The earliest histologic investigation of the skin in pellagra which was available to us was that of Raymond,[1] who in 1889 studied the skin from an atrophic lesion on the back of the hand of a patient with chronic

These studies were aided by grants from the John and Mary R. Markle Foundation and Anheuser-Busch, Inc.

From the Department of Pathology of the Washington University School of Medicine and the Barnard Free Skin and Cancer Hospital, St. Louis; the Department of Internal Medicine of the University of Cincinnati College of Medicine, Cincinnati, and the Nutrition Clinic of the Hillman Hospital, Birmingham, Ala.

1. Raymond, P.: Les altérations cutanées de la pellagre (la pellagre en Autriche), Ann. de dermat. et syph. **10**:627, 1889.

pellagra.[2] He found that the entire epidermis was atrophic but that the stratum corneum was thickened. The stratum granulosum was relatively normal. In addition to the extreme atrophy of the rete and the concomitant flattening of the rete pegs, Raymond found changes in the cells themselves. The cytoplasm of the cells was normal. The nuclei showed vesicular degeneration, which he considered to be the result of a "process of irritation" and vascular dilatation in the cutis. The elastic and collagenous fibers of the corium were normal, but a slight thickening of the entire cutis was observed. The hair follicles, the sebaceous and sweat glands and the peripheral nerves were unaffected.

Babes and Sion[3] (1901) were the first to study the various stages in the development of the lesions occurring in pellagra. They found that the erythematous stage was marked by a slight serous exudation and an infiltration of leukocytes. They also described peculiar homogeneous metachromic masses of what they considered to be coagulated albumin. In the stage of desquamation and hyperkeratosis an infiltration of lymphocytes, plasma cells and a few mast cells was present in the interpapillary pegs of the corium. The fibrils of the elastic tissue in the superficial part of the cutis were thought to show evidence of swelling and degeneration. The thickening of the skin was considered to be due to increased blood supply. The sweat glands were atrophic. The changes described in cases in which ulcers developed in the skin were those of any chronic ulceration. They also found rodlike structures in the corium which they interpreted to be bacteria, etiologically related to the disease.

One of the first histologic studies of pellagra in the United States was that of Gurd[4] (1911), who secured skin from the forearm and the dorsum of the foot in 11 cases at autopsy. He felt that the earliest cutaneous lesion was an erythema, sometimes accompanied by a loss of collagenous fibrils and degeneration of the elastic tissue of the superficial layers of the corium. Following this degeneration, a reparative change was evidenced histologically by an increased cellularity in the corium and an infiltration of lymphocytes and plasma cells. The capillaries were also dilated and increased in number. The hyperplasia of the squamous layer and of the stratum granulosum was thought to be the result of this increased vascularity. He considered that the cause of

2. Raymond[1] referred to the work of Griffini, which he believed to be one of the earliest descriptions of the pathologic changes in the skin in pellagra.

3. Babes, V., and Sion, V.: Die Pellagra, in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1905, vol. 24, pt. 2, no. 3.

4. Gurd, F. B.: A Histological Study of the Skin Lesions of Pellagra, J. Exper. Med. **13**:98, 1911.

the initial degeneration in the cutis was an irritant, possibly sunlight, acting in the presence of an undefined predisposing factor.

Corlett and Schultz [5] (1911) studied the skin from the "inner aspect of the radial side of the wrist" in a case of pellagra which came to autopsy. In addition to the atrophy of the epidermis, the swelling of the collagenous fibers and the disappearance of elastic fibrils in the superficial layers of the cutis, these investigators described marked chronic inflammatory and degenerative processes in the nerves of the corium. These changes in the nerves they thought to be the primary lesion in the skin.

As a part of the investigation of the Pellagra Commission of the State of Illinois, Ormsby and Singer [6] (1911) studied skin from 8 cases of pellagra. They felt the general picture was that of an angioneurotic process, resembling that seen in erythema multiforme. They described in the epidermis hyperkeratosis and parakeratosis together with a practically normal stratum granulosum and rete. Large amounts of pigment were present in the epidermis. The upper portion of the corium showed an inflammatory reaction, and the connective tissue appeared edematous.

MacNeal [7] (1921) pointed out that various stages in the cutaneous eruption may be represented in different areas in one person at the same time. He thought that the cutaneous lesions were perhaps the result of a toxic irritant carried by the blood or lymph to which the epidermis was particularly sensitive.

Crutchfield [8] (1928) examined histologically skin removed at autopsy in 10 cases. He found that the early lesions were those of inflammatory infiltration and that these were followed by atrophy. None of the changes studied were considered pathognomonic of pellagra.

Only recently Smith, Smith and Callaway [9] studied the sebaceous glands in 512 pellagrins, and they observed clinically a so-called "dyssebacia" in 61 patients. They reported the results of microscopic examination of skin from the face of a patient with this condition. Hyperplasia of the sebaceous glands was present throughout the corium. There

5. Corlett, W. T., and Schultz, O. T.: Pellagra in Ohio, with Report of a Case, J. Cutan. Dis. **29**:193, 1911.

6. Ormsby, O. S., and Singer, H. D.: Clinical and Pathological Studies, in Report of the Pellagra Commission of the State of Illinois, Springfield, Ill., Illinois State Journal Company, State Printers, 1911, pp. 16-43.

7. MacNeal, W. J.: Pellagra, Am. J. M. Sc. **161**:469, 1921.

8. Crutchfield, E. D.: Pellagra with Special Reference to the Skin and Mucous Membranes, Arch. Dermat. & Syph. **17**:650 (May) 1928.

9. Smith, S. G.; Smith, D. I., and Callaway, J. L.: Dysfunction of the Sebaceous Glands Associated with Pellagra, J. Invest. Dermat. **4**:23, 1941.

was extreme hyperkeratosis, but the epidermis was of normal thickness with some flattening of the rete pegs. Follicular dilatation and plugging of the hair follicles with dry sebaceous material were observed. The corium showed moderate edema with a slight round cell infiltration. The sweat glands were normal.

As a result of these and numerous other less detailed studies the consensus is that the initial cutaneous lesion of pellagra consists of an inflammatory reaction, which may or may not be accompanied by the formation of vesicles or bullae. This stage is followed by hyperplasia of the epidermis with hyperkeratosis and an increase in pigment throughout the layers of the epidermis. Pigment granules are found even in the stratum corneum. Accompanying edema and dilatation of blood vessels are found in the corium. The end stage of the process is that of atrophy of the epidermis with flattening of the rete pegs and fibrosis of the cutis.

No studies of the clinically unaffected skin of pellagrins have been reported heretofore.

## MATERIAL AND METHODS

Biopsy specimens from clinically affected and unaffected areas of skin were obtained from 15 patients with clinical pellagra at the Hillman Hospital in Birmingham, Ala. The specimens from the pellagrous lesions were taken from the skin of the left forearm, with the exception of one which was taken from the right leg. The specimens from the unaffected areas were taken from the lower extremities or from the trunk.

All of the tissues were fixed in 4 per cent formaldehyde. Paraffin sections were prepared, and the sections from each case were stained with hematoxylin and eosin, Mallory's phosphotungstic acid-hematoxylin and Van Gieson's trinitrophenol and acid fuchsin.

In every instance the patients from whom the specimens were secured reacted favorably to the administration of nicotinic acid. This supports the general assumption that the lesions described are due to vitamin deficiency and are not the result of some related deficiency seen frequently in pellagrins.

## OBSERVATIONS

One of the most striking changes found in the specimens from pellagrous lesions was the hyperkeratosis, which was present in all the cases studied (fig. 1). The specimens of unaffected skin removed in these cases also showed hyperkeratosis. With the exception of 1 case, it was less evident in the tissue removed from areas which showed no gross evidence of pellagrous change than in skin from actual lesions. In 4 cases plugging of the necks of the hair follicles with masses of

keratin was noted in tissue from the pellagrous lesions (fig. 2), while in specimens from unaffected areas changes in the hair follicles were not observed. In 4 specimens from pellagrous lesions patchy areas of parakeratosis were also found. Such areas were not present in the unaffected skin. The granular layer was more frequently thickened in the tissue removed from pellagrous lesions than it was in that from unaffected areas, and in some of the specimens from active lesions the granular layer was discontinuous.

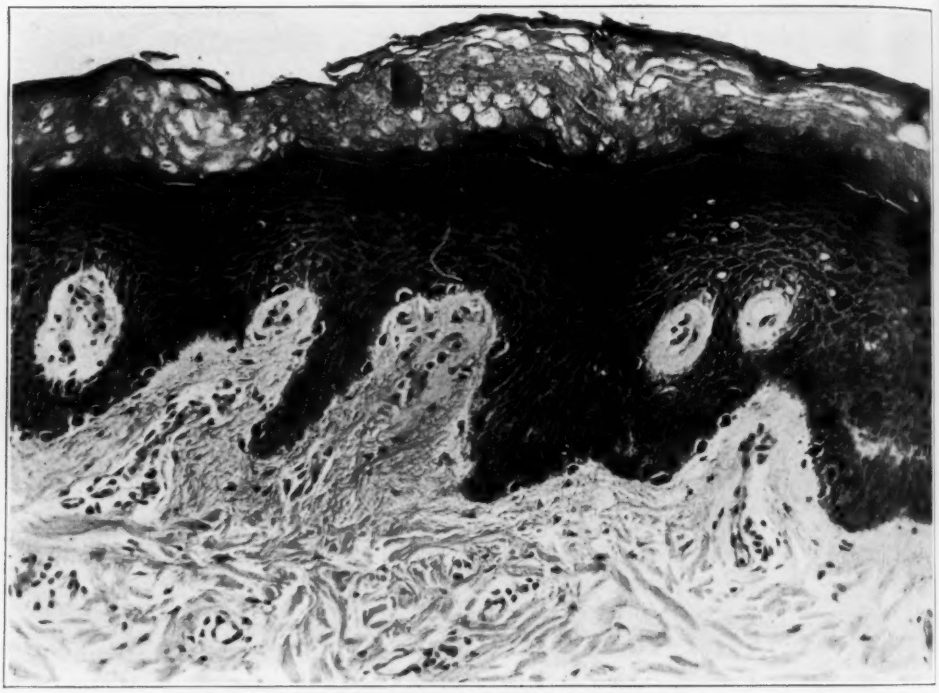

Fig. 1.—Low power photomicrograph of the skin from a pellagrous lesion, showing in the epidermis hyperkeratosis and acanthosis with lengthening and fusion of the tips of the rete pegs and in the cutis edema of the interpapillary portion with a moderate lymphocytic infiltration.

Most of the specimens from the pellagrous lesions showed marked acanthosis. In only 4 cases this change did not show to at least some degree, and, of these, in 2 there was atrophy of the epidermis and in 2 limited foci of atrophy (fig. 3). This varying microscopic picture may be attributable to the stage of the disease at which the specimens for biopsy were taken. None of those from the unaffected skin showed acanthosis. Most of them, on the contrary, showed foci of atrophy and

some an extensive atrophy over the entire section (fig. 4). In those cases in which the skin from affected areas was atrophic, that from unaffected areas showed a similar change.

Vesicles were never found in the tissue removed from unaffected skin, but in 5 cases vesicles were present in the skin from pellagrous lesions (fig. 5). These were usually located at the dermal-epidermal junction. The epidermis about the vesicles was edematous, and in 2 cases neighboring areas of necrosis with ulceration were found.

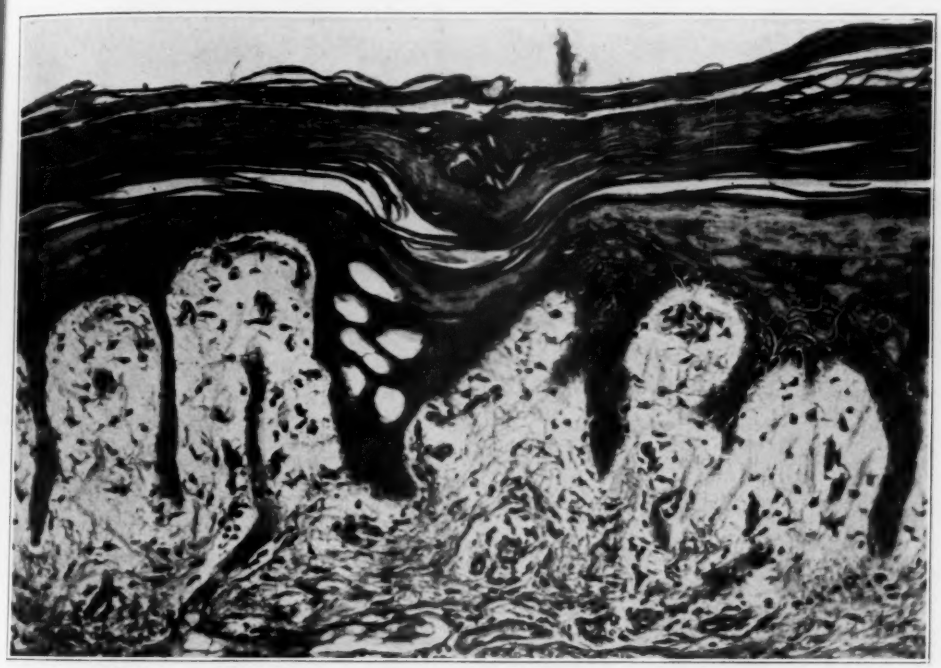

Fig. 2.—Low power photomicrograph of the skin from a pellagrous lesion, showing in the epidermis hyperkeratosis and parakeratosis with atrophy of the spinous layer and thinning and lengthening of the rete pegs and in the cutis edema of the interpapillary and subpapillary portion and a moderate lymphocytic infiltration. The mouth of a sweat gland duct is shown, which is plugged with keratin and dilated.

In general, more pigment was present in the epidermis of specimens obtained from pellagrous lesions than in those from unaffected skin. Moreover, the pigment was distributed more widely throughout the layers of the epidermis. Deposits of pigment could be found even in the hyperkeratotic stratum corneum in 2 cases (fig. 1). In 1 case in which the skin from the pellagrous lesion was atrophic there was loss of pig-

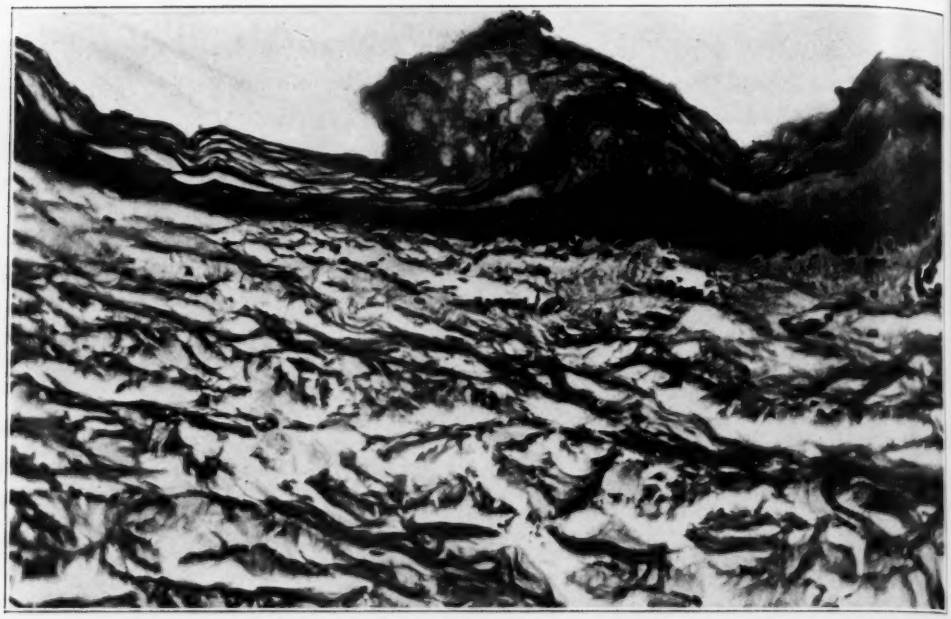

Fig. 3.—Low power photomicrograph of the skin from a pellagrous lesion, showing in the epidermis hyperkeratosis and atrophy and in the cutis edema.

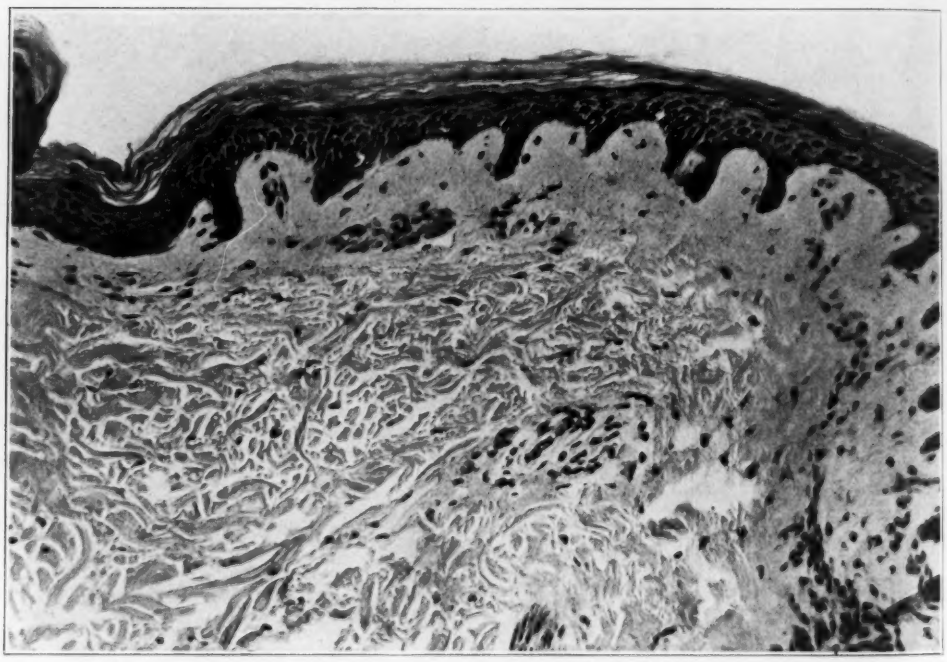

Fig. 4.—Low power photomicrograph of the skin from a clinically uninvolved area in a patient with pellagra, showing hyperkeratosis and atrophy and also slight edema and lymphocytic infiltration of the cutis.

ment from the epidermis, while the skin from an unaffected area in the same case was relatively normal except for a slight hyperkeratosis.

In the histologic sections from both pellagrous lesions and unaffected skin, edema of the collagen of the cutis was decided. The changes in the corium in pellagrous lesions varied from a moderate swelling of the individual fibers to hyalinization and mucoid degeneration with necrosis of fibers in the deeper part of the corium. In the specimens from unaffected areas the edema of the collagen, although definite, was less evident. In

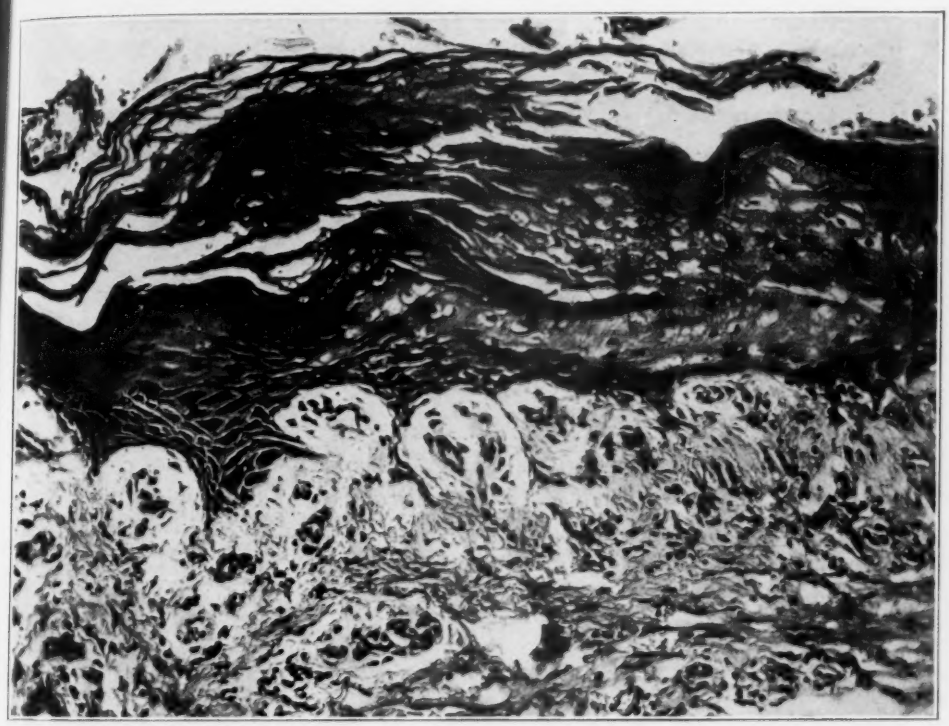

Fig. 5.—Low power photomicrograph of the skin from a pellagrous lesion, showing an early intraepidermal vesicle. The epidermis shows hyperkeratosis and the interpapillary portion of the cutis, edema with consequent distortion of the rete pegs of the epidermis.

the pellagrous lesions the blood vessels of the cutis were dilated, but in skin from the unaffected areas such changes in the vessels were not observed. In all but one of the specimens from affected areas, a lymphocytic infiltration was present in the interpapillary portion of the cutis and about the blood vessels. In 4 cases there was as pronounced an infiltration in the skin from unaffected areas as in that from the pellagrous lesions.

The changes in the sebaceous glands, both in the affected and in the unaffected skin, were of interest. In the tissue from the pellagrous lesions in 8 of the 15 cases the sebaceous glands were either atrophic or entirely absent. The skin from the unaffected areas showed similar changes in 4 cases. There was no correlation, however, between the two groups of specimens. The cytoplasm of the epithelial cells of the atrophic glands was vacuolated, and the nuclei were pyknotic.

The sweat glands were essentially normal both in the skin from the clinically manifest lesions and in that from unaffected regions. The stroma about the sweat glands was edematous in the specimens obtained from the pellagrous lesions. In the tissue from unaffected areas this change was not noted. The cutis as a whole was less edematous in the unaffected areas.

## COMMENT

The microscopic picture of the lesions of pellagra is similar to that found in chronic inflammatory diseases of the skin. In eczema, for example, the primary changes are edema, parakeratosis and acanthosis in the epidermis and vascular dilatation, edema and cellular infiltration in the corium. Epidermal vesicles occur in eczema as in pellagra. In eczema, however, no increase in pigment is found, such as is present in some cases of pellagra, and there is no end stage of atrophy. The pathologic picture in neurodermatitis (atopic dermatitis) is also somewhat similar to that found in pellagra. The cutaneous lesions of neurodermatitis show hyperkeratosis and parakeratosis, and the epidermis is edematous and irregularly acanthotic. The basal layer may contain an increased number of pigment granules. The corium shows some edema and moderate dilatation of the blood vessels. A perivascular cellular infiltration, which consists largely of lymphocytes with a few mast cells and eosinophils, is present in the cutis. Vesicle formation occurs rarely, however, and there is no atrophy of the epidermis in healing lesions, such as is found in pellagra. In the so-called "erythema group" of cutaneous diseases, especially in erythema multiforme, pathologic changes similar to those in pellagra may also occur. Ormsby [10] characterized erythema multiforme as essentially "a hyperemia of the integument that under certain influences advances more or less rapidly to the stage of a mild grade of inflammation, with consequent exudation." Edema of the corium with dilatation of the blood vessels and with a perivascular infiltration made up predominantly of lymphocytes is a fairly constant finding. If an increase in pigment were not present in a pellagrous lesion, microscopic sections of pellagrous skin could probably be distinguished only with difficulty from those of lesions of erythema multiforme.

10. Ormsby, O. S.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1937, p. 133.

Whether or not the unaffected skin shows pathologic change in most of these chronic inflammatory cutaneous diseases is not known, for there are few studies of the so-called normal skin of patients who present localized cutaneous lesions. As early as 1906 Engman and Mook [11] studied the unaffected skin in 4 cases of epidermolysis bullosa and described definite pathologic changes: in the epidermis, edema and colliquative degeneration of the basal layer; in the cutis, edema and dilatation of the blood and lymph vessels, and in the papillary and subpapillary regions, a complete absence of elastic tissue. This early study was not followed by similar work on other diseases until recently. MacCardle, Engman and Engman [12] have just completed a study of the unaffected skin in cases of neurodermatitis, using in addition to the ordinary histologic methods spectroscopy and microincineration. They have found that the clinically unaffected skin shows pathologic changes similar to those found in the active lesions, although the degree of change is less. One of the most interesting findings is the decrease in magnesium which was demonstrated by microincineration and spectrography in the unaffected as well as the affected skin. Madden [13] reported at the last meeting of the American Dermatological Association a histologic study of the uninvolved skin in psoriasis; he found microscopic evidence of pathologic change in the clinically unaffected skin of persons with this disease. Thus, it is becoming increasingly apparent that chronic diseases of the skin may affect the entire integument of the patient even when clinical evidence of involvement is lacking. The present study of the clinically uninvolved skin in pellagrins supports this view.

The skin from both clinically affected and unaffected areas in pellagrins was hyperkeratotic. Parakeratosis was also found in the actual lesions. Thus, one of the most striking pathologic processes occurring in pellagra is a disturbance of keratinization. The normal process of cornification is dependent on the deposition of granules of keratohyalin in the cells of the granular layer. It is generally assumed that the deposition of eleidin in the stratum lucidum also plays a role in the normal process of keratinization. MacLeod [14] considered keratohyalin to be "a separa-

11. Engman, M. F., and Mook, W. H.: A Study of Some Cases of Epidermolysis Bullosa, with Remarks upon the Congenital Absence of Elastic Tissue, J. Cutan. Dis. **24**:55, 1906.

12. MacCardle, R. C.; Engman, M. F., Jr., and Engman, M. F.: (*a*) Histology of Neurodermatitis, Arch. Dermat. & Syph. **44**:161 (Aug.) 1941; (*b*) Spectrographic Analysis of Neurodermatitis Lesions: A Human Magnesium Deficiency, ibid. **44**:429 (Sept.) 1941; (*c*) Mineral Changes in Neurodermatitis as Revealed by Microincineration, ibid., to be published.

13. Madden, J. F.: Histologic Studies of Uninvolved Skin of Patients with Psoriasis, Arch. Dermat. & Syph. **44**:655 (Oct.) 1941.

14. MacLeod, J. M. H.: Handbook of the Pathology of the Skin, London, H. K. Lewis, 1903, p. 72.

tion product of the protoplasm of the cell which appears as the vitality of the cell is diminishing; eleidin, a further product of the same substance; and the ultimate product of both, probably the fatty or waxy substance which is present in the horn cells." This ultimate product is keratin, which is now known to be an albuminoid, and at least two keratins are known to exist. A satisfactory explanation of the mechanism of keratinization has not been made. It is becoming more and more evident, however, that vitamin deficiencies affect the process. As early as 1925 Wolbach and Howe [15] in an investigation of avitaminosis A in rats produced keratinization in epithelial cells which were not normally keratinized. Recently some of the clinical dyskeratoses have been shown to respond to treatment with this vitamin (pityriasis rubra pilaris [16] and keratosis follicularis [17]). Apparently a deficiency in the vitamin B complex also produces a disturbance in keratinization, such as is evidenced by the hyperkeratosis found in both clinically affected and unaffected skin in pellagrins. The process is more evident in the actual lesions where parakeratosis is found. Ormsby attributed parakeratosis to edema occurring in and between the rete cells, which interferes with the formation of keratohyalin in the granular layer. The cells of the corneal layer appear swollen and moist, stick together instead of being normally shed and retain their nuclei. The formation of keratin is prevented. Thus, perhaps the deficiency of nicotinic acid in pellagrins affects the granular layer in such a way as to interfere with the normal production of keratohyalin. This process might be looked on as the result of the absence of a maturation factor.

The acanthosis which is present in the skin from pellagrous lesions, and not present in the unaffected skin may be due to edema. It may also be caused by an increased proliferation of the cells of the spinous layer. Thuringer [18] has shown that these cells normally divide. He found in measured areas of epidermis of the scalp, obtained at executions, 12 per cent of the total number of mitotic figures in the basal layer, 30 per cent in the lower third of the spinous layer, 46 per cent in the middle third and 12 per cent in the outer third. Similar figures were obtained in a study of mitosis in the skin of the prepuce.[18] Although no increase in

15. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamine, J. Exper. Med. **42**:753, 1925.

16. Brunsting, L. A., and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. **43**:42 (Jan.) 1941.

17. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis: A Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223 (Feb.) 1941.

18. Thuringer, J. M.: Regeneration of Stratified Squamous Epithelium, Anat. Rec. **28**:31, 1924; Studies on Cell Division in the Human Epidermis: II. (*a*) Rate of Cell Division in the Prepuce; (*b*) Influence of Various Factors on Cell Division, ibid. **40**:1, 1928.

the number of mitotic figures could be demonstrated in the acanthotic areas of the epidermis in pellagrous lesions, it is conceivable that such a proliferation of cells could occur.

No satisfactory explanation of the atrophy which is present both in healing pellagrous lesions and in the unaffected skin can be given. That atrophy occurs normally with aging of the skin and that it may result from either external or internal pressure has long been known, but the exact mechanism involved in the process remains unexplained, and the present study affords no new information concerning it.

Edema of the corium and a moderate infiltration of lymphocytes were found in both the affected and the unaffected skin in pellagra. As Ormsby pointed out, some degree of the process recognized as inflammation is present in most of the cutaneous diseases and consists of vascular dilatation, infiltration of cells and exudation of plasma. The leukocytes, attracted by positive chemotaxis to the point of irritation, either remove the offending material by phagocytic action or themselves undergo degeneration. The chemotactic agent may be a mechanical, chemical or thermic irritant or a product of cellular metabolism. Apparently some irritant, possibly chemical in nature, is present not only in the clinically pellagrous lesions but in the entire skin of patients with the disease.

## SUMMARY AND CONCLUSIONS

The pathologic changes found in both the clinically affected and the unaffected skin of patients with pellagra consist primarily of dyskeratosis and atrophy of the epidermis and inflammation of the cutis. Since the skin reacts favorably to treatment with nicotinic acid, it would seem that these changes are to a considerable extent reversible and that they may represent a specific response on the part of the skin to a deficiency of this part of the vitamin B complex.

Washington University School of Medicine, St. Louis.
Hillman Hospital, Birmingham, Ala.
Barnard Free Skin and Cancer Hospital, St. Louis.

# TREATMENT OF SENILE PRURITUS WITH ANDROGENS AND ESTROGENS

SAMUEL FELDMAN, M.D.

JULIUS POLLOCK, M.D.

AND

A. ROBERT ABARBANEL, M.D.

NEW YORK

During the course of our study of the effects of treatment of senile vulvovaginitis, leukoplakia and kraurosis vulvae with estrogens, we observed the beneficial effect that the treatment had not only on the local lesions but on the pruritus which was usually present. In practically every case there was a diminution or disappearance of the itching and with it of the scratch marks and local irritation. This led us to believe that in at least some of the cases of senile pruritus the itching was caused by local or constitutional changes incidental to a sex hormone deficiency.

We decided to make an attempt to verify our belief by treating some of our elderly patients who suffered from pruritus with estrogens and androgens. Fortunately, we had the material at hand and proceeded to select our cases, but this was beset with numerous difficulties. Not all elderly persons with thin, dry and atrophic skins are afflicted with pruritus. It may happen that itching develops in one of these persons from one or more of a multitude of causes which are not quite evident at the time and are not at all due to senile changes. Senile pruritus may be erroneously blamed for it; and if the patient were treated with an endocrine product failure would be the inevitable result and the failure would be attributed to inadequacy of endocrine medication. Senile pruritus may be associated with other pathologic conditions which are capable of producing itching of their own accord. A good example is the frequent presence in old persons of edema and eczema of the legs due to prolonged hypostasis from poor local circulation. Lastly, one must learn to estimate the part played by scratching and irritating an already damaged skin in producing such lesions as patches of eczema, lichenification and hyperpigmentation. It is logical to assume that these lesions will respond to the kind of treatment which will relieve the

From the Department of Dermatology and Pathology, Morrisania City Hospital, and the Department of Dermatology and Clinical Pathology, Home and Hospital of the Daughters of Jacob.

itching. This actually has happened. Even eczema of the legs caused by hypostasis shows a certain amount of improvement with the subsidence of the generalized itching.

There is no certain way of making a diagnosis of senile pruritus. With the exception of the degenerative changes produced by the action of sunlight on the exposed surfaces of the skin in old persons, the pathologic changes are not sufficiently characteristic to be taken as a criterion. Neither does the clinical appearance of the skin offer anything valuable from the standpoint of diagnosis; at most, it can be only suggestive.

Creatinuria has been advanced as a means of diagnosis of androgen deficiency. Normal males do not excrete creatine in the urine. That substance is converted into creatinine before excretion. Steinach, Kun and Peczenik [1] stated that if the amount of creatine is 10 per cent or more of the total creatine and creatinine in the urine, a real androgen deficiency exists.

### ANDROGENS AND ESTROGENS

These sex hormones are members of a group of hydrogenated phenanthrene derivatives known as the sterols. The best known example of this group is cholesterol. Ergosterol, derived from ergot and a precursor of vitamin D, is another well known example. In the laboratory androgens and estrogens are produced from cholesterol. It is thought that in the body also they are produced from cholesterol, although it is possible that they may also be derived from the carotenoids and vitamin E. The most active androgen, testosterone, is derived from the testis. Estrogen, or female sex hormone, is derived from the follicles of the ovary. Both estrogens and androgens are found in the urine of both sexes, only in varying amounts.

Injections of estrogens in the male cause an interference with spermatogenesis and an enlargement of the breast. Injections of androgens in the female cause a suppression of the menstrual cycle, a change in the vaginal epithelium to the atrophic menopausal type, deepening of the voice, hirsutism and an enlargement of the clitoris. This action is thought to be not a direct antagonism but due to the gonadotropic activity of the pituitary gland. Injections of androgens in castrates produce a sustaining effect on the sex organs. When estrogens are added to the androgens, the effect is much greater. Here synergistic action of the hormones of the opposite sexes is seen. For that reason, one can no longer regard them as entirely sex specific. It is possible that the difference in the action of these endocrine factors

1. Steinach, E.; Kun, H., and Peczenik, O.: Diagnostischer Test für hormonbedingte Störungen der männlichen Sexualfunktion und seine klinische Anwendung, Wien. klin. Wchnschr. **49**:388, 1936.

in the two sexes depends on the difference in the tissues and organs on which they act. Tadokoro [2] claimed to have found such differences in the sexes, particulary in the proteins of the muscle and skin. These differences reside in the histidine, arginine and cystein content. He reported these differences in the protein content of the hide of cows and bulls. He claimed that the myocin and myogen fractions from the muscle tissue of the capon two months after castration approach in composition the corresponding muscle protein from the hen.

## REPORT OF CASES

CASE 1.—M. F., a Russian Jew aged 86,[3] who was formerly a cantor, was admitted to the Home and Hospital of the Daughters of Jacob on Jan. 3, 1929. He had enjoyed comparatively good health until about three years previously, when generalized itching developed. There had been several remissions of the itching for short periods, but with any and all types of treatment which the patient received there was little or no relief from his suffering. During the past few months the itching had become more annoying. This was particularly intense on the extremities.

On examination on Oct. 14, 1940, the skin appeared to be considerably thinned, shiny and unduly wrinkled. There was a mild follicular keratosis. Scratch marks were present all over the body. The patient appeared well preserved for his age, and his mental processes were excellent.

Laboratory examination of his blood and urine showed no abnormalities. The results of chemical examination of his blood were within normal limits.

On October 19 10 mg. of testosterone propionate was injected subcutaneously, and 10 mg. more was injected on October 30. There was no noteworthy change until November 4, two weeks after the first treatment, when the patient stated that except on the extremities there was a considerable amelioration of the itching. Five milligram doses were given every five days until Jan. 11, 1941, at which time the patient stated that there was only occasional mild itching of his legs. Treatment was discontinued.

The patient remained symptomless until February 20, when a slight itching developed on his scalp and legs. Ten milligrams of testosterone propionate was injected subcutaneously, followed by 5 mg. every five days thereafter. The patient continued to improve, and on March 15 the itching had entirely disappeared.

There was no pruritus until April 26, when a slight itching of the lower extremities developed, and by May 6 there was also itching of the scalp, neck and chest. Ten milligrams of testosterone propionate was injected, and this dose was repeated on May 13 and June 9. By that time the patient was again entirely free from itching. The last injection was given on June 16, and treatment was for the time being discontinued.

Because of the finding of a number of observers that the presence of creatine in the male urine indicates an androgen deficiency, we were desirous of ascer-

2. Tadokoro, T.: Sex Difference from the Standpoint of Biochemistry. J. Fac. Sc. Hokkaido Imp. Univ. **1**:1, 1930; **1**:185, 1933; **2**:13, 1934.

3. Presented at a meeting of the Bronx Dermatological Society, Feb. 27, 1941 (Arch. Dermat. & Syph. **44**:714 [Oct.] 1941).

taining what happened with the metabolism of creatine and creatinine in our patients before and after treatment. The urine voided during a period of twenty-four hours was collected and tested for these substances quantitatively.

It is unfortunate that we were unable to collect the urine of this patient before treatment was instituted. The old people in the institution are willing to cooperate with the medical staff, yet it is nearly impossible at times to receive their full cooperation in this particular respect.

There was no creatine present after the first course of treatment, and the creatinine amounted to 1.43 Gm. per day. His urine was tested again after the symptoms returned, and there was practically no change.

Because of the presence of a mild follicular keratosis and because it was suggested that that might indicate a vitamin A deficiency, the patient at this time was given vitamin A by oral administration. The average daily dose was about 125,000 U. S. P. units. The itching continued and became gradually worse, so that after a little over two weeks of vitamin A medication we were compelled to return to the endocrine therapy.

CASE 2.—M. F., a Russian Jewish housewife aged 82.[3] was admitted to the Home and Hospital of the Daughters of Jacob in December 1939. At that time she complained of a generalized itching, which she had had for a long time but which had become severe during the past two years. It was most intense in the genital region. She had five children, and her last menstrual period was at the age of 50.

Her skin appeared to be loose, thin, wrinkled and slightly scaly. There were few scratch marks. The vaginal tract appeared to be smooth, pearly white and dry.

On Sept. 25, 1940 examination revealed that the condition and appearance of the skin and vulvar mucosa were about the same as on admission. A vaginal smear taken at that time showed occasional epithelial cells with small nuclei. The rest of the cells were mainly white blood cells. Her mind remained clear, but she had been suffering from arteriosclerosis and chronic myocarditis.

Her urine was normal, and chemical examination of her blood showed no abnormalities. The blood picture was that of pernicious anemia, for which the patient was being treated with injections of liver extract.

On September 30 10 mg. of testosterone proprionate was injected subcutaneously. The dose was repeated every five days until November 4, with no improvement either in the generalized itching or in the genital pruritus. There was no change in the vaginal smear. Treatment with testosterone was discontinued, and estradiol dipropionate, an estrogen, was substituted, in doses of 1 mg. subcutaneously every five days. After two injections the itching of the skin and genitalia was greatly reduced. On November 25, three weeks after the change in treatment, the patient stated that the itching had enirely disappeared. The treatment was continued once a week with injections of 1 mg. of the substance. On December 25 a vaginal smear showed numerous epithelial cells with large nuclei and only an occasional leukocyte.

The patient was entirely free from symptoms until Feb. 23, 1941, when a mild itching again developed. She was given an injection of 1 mg. of estradiol dipropionate, and this was repeated once a week. There was considerable improvement, but in order to test the specificity of the effect of the estrogen on the itching, administration of that drug was discontinued and 1 cc. of sesame oil was used instead, care being taken that the patient should not know of the change. A total of four injections, one every seven days, was given. The itching became gradually worse, and on March 31 it was intense. One milligram of estradiol

benzoate was injected on April 7, and this dose was repeated once a week. Six weekly injections of the new preparation produced little effect on the general pruritus. There was, however, an amelioration of the vaginal itching.

When this patient was presented at a meeting of the Bronx Dermatological Society it was suggested that she be given injections of some neutral substance in order to exclude a possible psychic influence of the injection on the pruritus. Sesame oil was selected because that substance was used as a solvent for the estrogen. The result obtained should leave no doubt in one's mind that the oil had no influence on the itching.

During the course of treatment of this patient another fact was demonstrated, namely, that the benzoate of estradiol is either impotent as a remedy for senile pruritus or it is much weaker in its action generally, presumably because of the fact that that preparation is absorbed and excreted too rapidly.

On May 22 treatment with the benzoate was discontinued, and injections of 1 mg. of estradiol dipropionate were given once a week. There was improvement after the second injection, and she was completely free from itching on June 20.

Case 3.—A. F., a Russian Jew aged 87, formerly a tailor, was admitted to the Home and Hospital of the Daughters of Jacob on Nov. 19, 1940. He stated that he was married and that his wife was alive and well. He had four living children, the youngest being 48 years old. He was suffering from generalized arteriosclerosis and mild parkinsonism. For the past three years he had suffered from a severe itching of practically the whole body. The itching was more intense on the lower extremities, and there were some remissions and exacerbations.

This patient's skin was obviously senile. There was a noticeable dryness. The skin was lax and deeply wrinkled and in places had a cigaret-paper-like appearance. Except for an acute dermatitis, which was restricted to his legs, and universally scattered scratch marks, there were no visible lesions.

His urine and blood, including results of chemical examination of the blood, were normal.

On November 27 10 mg. of testosterone propionate was injected subcutaneously. The patient was hospitalized on account of his dermatitis, and the injections were repeated every five days thereafter. The patient stated that he experienced great relief from his itching after the third treatment. On December 30, the generalized itching had completely disappeared and the dermatitis was greatly improved. He was then allowed to get out of bed, and he had a relapse of the dermatitis of the legs; but his generalized itching did not return until Feb. 20, 1941 when a slight itching of the body returned and became worse by March 15. On March 19 1 cc. of sesame oil was injected as a control. This was repeated once a week. The patient's condition became worse and continued so until April 16, when he was again given 10 mg. of testosterone propionate subcutaneously. The injection was repeated on April 24. The patient stated that the improvement began shortly after the first injection of the estrogen. On May 13, when he received another 10 mg. of testosterone propionate, all symptoms had disappeared. Only a mild dermatitis of the legs remained. The treatment was continued until June 16, at which time the itching had entirely disappeared. The patient remained without symptoms until July 8, when the itching began to recur.

CASE 4.—M. C., a Jew aged 82, born in Russia, was an inmate of the Home and Hospital of the Daughters of Jacob. He complained of severe itching for the past five years. He stated that he enjoyed comparatively good health. He had been married and had seven children, six of which were living and well. He had a dermatitis in 1939, which had subsided after local medication and seven weekly roentgen ray treatments. The itching, however, was unrelieved by either local medication or sedatives taken internally. The patient was mentally well preserved. He had arteriosclerosis and asthmatic attacks.

The skin was visibly thin and atrophic. There was an evident loss of elasticity. When the skin was pinched between the thumb and index finger, a fold remained for some time before the skin returned to normal. Several patches of dermatitis with infiltration and lichenification were present on the extremities, and scratch marks were seen everywhere. Numerous hyperpigmented areas were seen all over the body.

There were no abnormalities in the urine or the blood, either chemically or microscopically.

Ten milligrams of testosterone propionate was injected on Sept. 30, 1940, and 10 mg. more on October 4 and every five days thereafter.

On October 9 the itching was less severe. On October 19, except for having a slight itching on the scalp and legs, the patient was entirely comfortable. He received no other medication, either locally or by mouth; yet the dermatitis gradually improved. By November 4, when another 5 mg. of testosterone was injected, there were only a few lesions present on the legs, and these appeared to be smaller, smoother and less infiltrated. Except in these lesions, the itching completely disappeared. The depth of pigmentation was also lessened considerably. Treatment was continued, and there were no recurrences of the itching until November, when the patient died of a heart attack.

CASE 5.—B. G., a Jew aged 76, was a Russian by birth. His former occupation was that of a broker. He was admitted to the Home and Hospital of the Daughters of Jacob on July 14, 1938. He stated that, except for minor ailments in his early and adult life, he had enjoyed comparatively good health.

In midsummer of 1939 a severe generalized itching developed. This was particularly intense on his extremities and genitalia. During the past two months the itching was so severe that it interfered with his sleep.

On examination, the skin appeared to be thinner than usual and finely wrinkled, and there was a fine, almost imperceptible scaliness on the thighs, abdomen and back. A number of scratch marks were found scattered over the body, particularly on the extremities. He was suffering from a generalized arteriosclerosis but was mentally sound.

The urine was normal. The red and white blood cell counts and the hemoglobin content were within normal limits, and the blood on chemical examination was normal.

On Sept. 11, 1940 a pellet of 20 mg. of testosterone propionate was inserted subcutaneously. There was no improvement during the first week; but on September 19 the itching was much milder, and on September 24 the pruritus had completely abated. The patient has been free from any discomfort to date.

On March 15, 1941 there was still a small subcutaneous nodule where the pellet was inserted. A roentgenogram of the nodule showed complete absence of any signs of calcification.

It is remarkable the length of time one pellet can remain embedded in the tissues and continue to be effective as a therapeutic agent supplying

the necessary amount of estrogen. In the case of desoxycorticosterone in the endocrine treatment of Addison's disease, it is claimed that the duration of its effectiveness may be as long as twelve months.

At the time of writing, July 3, 1941, eight months has elapsed since the insertion of the pellet, and there is no return of symptoms.

CASE 6.—M. W., a white housewife aged 80, came to the dispensary of the Morrisania City Hospital on Nov. 18, 1940. She stated that she had suffered from generalized itching for the past ten years. Except for asthma, from which she had been suffering for the past three years, her general health was comparatively good.

The patient's skin appeared to be dry, scaly and wrinkled. There were a number of scratch marks, particularly on the forearms.

The blood and urine were normal, and the results of chemical examination of the blood were normal. She was given 10 mg. of testosterone propionate subcutaneously, followed by 5 mg. every week. After seven injections there was no improvement. On Jan. 2, 1941 administration of this drug was discontinued and 1 mg. of estradiol dipropionate was injected subcutaneously once a week. The patient felt relief from her itching on the third day after the first injection. The improvement continued, and there was practically no itching by January 28.

She did not appear for treatment until February 28 and stated that the itching had returned during the past four or five days. Her trunk was again a display of scratch marks.

She again received 1 mg. of estradiol dipropionate. This dose was repeated on March 3, when her itching was much improved and there were only a few scratch marks on her body. The patient had cardiac disease and appeared for treatment irregularly. Her next visit was on April 7. She stated that her itching became worse. Numerous scratch marks were again present. She received an injection of estradiol dipropionate and another on April 11. Her next visit was June 13, when the itching was as bad as ever. She stated, however, that her itching was much improved after the last treatment.

CASE 7.—A. M., a Jew aged 77, a tailor, came to the Morrisania City Hospital on Nov. 20, 1940. He was born in Hungary, was married and had eight children. His wife and children were living and well. He looked well preserved but suffered from arteriosclerosis and had occasional attacks of hay fever. Itching had developed on his entire body about one year previously. This had become worse in the last three months to the extent that it kept him awake nights.

His skin was dry, somewhat wrinkled and slightly scaly. Some scratch marks were present on his chest.

The urine and blood were normal, and the results of chemical examination of the blood were normal.

Ten milligrams of testosterone propionate was injected subcutaneously, followed by 5 mg. once a week. After the third treatment the patient stated that there was a notable improvement and that the night following the sixth injection was the first in the past year that he had slept through. He was completely free of itching after the eighth injection. Treatment was discontinued on Jan. 11, 1941.

On February 17 there was no itching, but on March 24 the patient said that there was a slight itching of his legs. However, the symptoms were so insignificant that we thought it best to keep him under observation for a while longer.

The patient was again seen on May 6. He stated that the symptoms began to return about April 20, and at the time of his visit the itching was fully developed, particularly on the chest and extremities.

A quantity of urine voided during twenty-four hours was collected and tested for creatine and creatinine with the following result: creatine 0.087 Gm. and creatinine 1.12 Gm.

He was given an injection of testotrerone propionate on May 6 and on May 12. He did not report to the clinic until June 13 and stated that he did not come to the clinic because he was completely comfortable and had no itching.

CASE 8.—B. R., a Russian Jew aged 88, formerly a peddler, was admitted to the Home and Hospital of the Daughters of Jacob on March 3, 1939 and gave the following history. He was suffering from generalized arteriosclerosis, parkinsonism and chronic myocarditis. He had had itching all over the body for the past fifteen years and a rash on his hands and feet for a number of years.

On examination, the skin was seen to be thin, wrinkled and shiny, and in certain locations there was a fine scaliness. Scratch marks were seen on the torso and extremities. Chronic eczema was present on his hands and feet, and a mild seborrheic dermatitis was present behind the ears and on the eyebrows. The itching was the most annoying complaint.

His urine and blood were normal, and the results of chemical examination of the blood were normal.

He was treated with every available local medication without the slighest relief. On Nov. 8, 1940 10 mg. of testosterone propionate was injected intramuscularly, followed by 5 mg every five days. After eleven treatments the improvement was of a doubtful nature. On February 20 the patient claimed that his condition was somewhat improved, but shortly after that there was a relapse and the itching was again as intense as it was in the beginning.

There was not enough improvement in this case to chart it as an instance of successful treatment, and we were about ready to admit that the therapy had failed. However, taking into consideration the possibility that some patients may require larger amounts of the androgen to be benefited, we decided to try more intensive medication. For that reason, a 20 mg. pellet of testosterone propionate was inserted subcutaneously on April 15. The patient showed signs of improvement after one week and continued to improve gradually. On May 29, when an additional 10 mg. of testosterone propionate was injected subcutaneously, the improvement was more rapid. On June 15 the patient felt well; he stated that both the burning and the itching sensation had disappeared. There was a decided improvement in the eczematous lesions on his head, face and extremities.

The patient was again examined on July 2, at which time there was not a single lesion on his skin.

To those who followed the course and progress in this case, the results appeared to be amazing, as it might appear incredible to one whose knowledge of the case is mere history. This case in particular should serve as an impetus for further study of the subject.

CASE 9.—M. O., an Austrian Jew aged 82, formerly a hat blocker, came to the dispensary of Morrisania City Hospital in November 1940 complaining of a severe generalized itching of three months' duration. The itching was worse at night. He was married and had four children. He had suffered from asthma and intermittent claudication in the lower extremities for the past ten years and had arteriosclerosis.

On examination the skin appeared to be white, dry, scaly, inelastic and wrinkled. There were numerous scratch marks.

His blood and urine were normal.

He was treated with ordinary methods without the slightest relief until Feb. 19, 1941, when 10 mg. of testosterone propionate was injected subcutaneously; this treatment was repeated every seven days. He began to improve after the first injection; and by March 24, after only four injections, the itching had entirely abated, but the treatments were continued until April 28.

On May 13 the patient complained of mild itching. To test still further the specificity of the effect of the endocrine medication, 1 cc. of a 1 per cent solution of procaine hydrochloride was injected, and on May 20 the patient stated that the condition was worse. Another ampule of procaine hydrochloride was injected, and the urine was tested for creatine and creatinine content. The former yielded 200 mg. in a twenty-four hour specimen and the latter 1.1 Gm.

At this juncture, after having treated 2 female patients with androgens in order to ascertain the specificity of the action of the endocrine substances on the sexes, we thought that this work should be supplemented with treating males with estrogens in order to ascertain the action of estrogen in senile pruritus in the male. For that purpose, 1 mg. of estradiol dipropionate was injected, subcutaneously on May 27 and again on June 3 and on June 10. There was no improvement in the itching, but, on the other hand, the pruritus did not increase, as was to be expected. No definite inference could be drawn from these results. Unfortunately, this experiment was interrupted by the patient's leaving town temporarily.

CASE 10.—A. E., a former housewife aged 80, was admitted to the Home and Hospital of the Daughters of Jacob on Feb. 20, 1941. She stated that she was married and had eight children. She had her menopause at the age of 40. She has never had any serious illness and appeared rather intelligent. She complained of severe itching during the past two years. The itching was generalized, but it was more severe in the genitalia.

She had senile skin, which was dry and wrinkled and was covered with numerous scratch marks. The vaginal smear showed numerous leukocytes and few small epithelial cells with small deeply stained nuclei. The vagina was smooth and grayish white.

One milligram of estradiol dipropionate was injected subcutaneously, and this treatment was repeated once a week. On March 19 the itching was much improved. The vagina assumed a more normal appearance, and the vaginal smear was nearly normal.

The injections were continued. On March 28 the patient began to show staining with blood from the vagina, slight at first but gradually increasing, and on March 31 there was moderate bleeding. There were no blood clots, and the gynecologist who examined the patient stated that there was no pathologic process and that the condition simulated normal menstruation. The injections were discontinued, and the bleeding gradually stopped. On April 16 there was absolutely no itching.

On April 25 the itching began to reappear. In order to avoid a possible attack of uterine bleeding, 0.5 mg. of estradiol benzoate, the preparation which in our experience proved to be weak in its action, was injected once a week for about five weeks. There was practically no improvement. On May 31 1 mg. of estradiol dipropionate was injected. This was followed by another injection

on June 7 and on June 13. At this time the itching was still severe and there was a recurrence of the vaginal bleeding. It seemed that this patient's reaction to the estrogen medication would prove a stumbling block.

In order to counteract the effect on the uterus, 10 mg. of testosterone propionate was administered in combination with 0.5 mg. of estradiol diproprionate on June 20, and 10 mg. of testosterone propionate and 1 mg. of estradiol dipropionate was injected on June 27. The bleeding stopped, but there was no relief in the itching. However, on July 12, after two more injections of the combined substances, there was a decided improvement, and on July 25, after six treatments with the combined substances, the patient was practically well.

CASE 11.—C. R., a Jewish housewife aged 63, came to the Morrisania City Hospital on Dec. 13, 1940. She stated that she had suffered from intense generalized itching for the past year. The itching was so severe that it made her at times "want to commit suicide." During the past year she had attended various dermatologic clinics, where she was treated with topical applications without any relief.

On examination the skin appeared to be practically normal except that there were numerous scratch marks on her chest and extremities.

Her blood and urine were within normal limits, and the results of chemical examination of the blood were normal. The urine contained 153 mg. of creatine and 1.2 Gm. of creatinine.

Treatment with local applications was continued until June 1, 1941. On that day 1 cc. of a 1 per cent solution of procaine hydrochloride was injected as a control. This had no effect on the itching. On June 4 1 mg. of estradiol dipropionate was injected. This was repeated on June 11 and June 18. The patient stated that she had considerable relief one week after the first treatment with the endocrine medication and that by June 15 the itching had entirely abated and from then on she slept through the nights without interruption. On July 16 the patient was still free from pruritus.

CASE 12.—I. B., a Jewish woman aged 76, had two children, the younger one 50 years old. She was admitted to the Home and Hospital of the Daughters of Jacob on April 25, 1939. She had essentially a normal past history. She was suffering from generalized arteriosclerosis and at the time of admission had an atrophic rhinitis. In January 1941 a generalized itching developed, which affected her entire body. It was severe enough to disturb her sleep, but she did not complain about it and for that reason remained without treatment until May 9. Her skin at that time was somewhat scaly and wrinkled, but there were no lesions present that could account for her itching.

Her blood count and hemoglobin were within normal limits. Her blood on chemical examination and her urine were normal. There was no creatine present in the urine voided during twenty-four hours, and only 0.89 Gm. of creatinine was present.

She was given 1 mg. of estradiol dipropionate subcutaneously. This was repeated on May 18 and 25 and on June 1. There was no improvement in the itching, but tenderness of the nipples developed. She continued to be treated regularly every week with the injections. The itching began to diminish about the beginning of July, and on July 25 the itching was slight but there was still some tenderness of the nipples. Treatment was continued, and on August 17 the itching had entirely subsided.

### MICROSCOPIC EXAMINATION

In each of the first 8 cases a small piece of tissue was removed from the outer surface of the thigh before treatment was administered. Another specimen was taken after completion of the first course of treatment, when the itching had entirely subsided. The sections were removed from areas as close to one another as possible. They were stained with hematoxylin and eosin and also with Weigert and Van Gieson stains for elastic tissue.

With almost no exception, all specimens which were removed before treatment presented the following picture: The corneal and granular layers were practically normal. The germinal layer was considerably thinner than normal, and the rete pegs were somewhat flattened. The cells of the stratum germinativum were poorly stained and were hazy in appearance. The papillae were flattened. There was a moderate amount of edema of the entire cutis. The collagenous bundles were swollen, were separated from one another by interfascicular edema and had lost their orderly arrangement. They stained poorly. The elastic tissue was diminished in amount, and there were fractioning and clumping in the middle and lower zones. There was a perivascular edema, and the outline of the vessels was indistinct and hazy. A small number of fibroblasts and round cells were found in the cutis.

The sections taken after the course of treatment was completed showed a decided reversion toward the normal. This was apparently evident, because when the sections were shown to Dr. W. Sachs, he was able to make out with ease which section was taken before and which after the treatment. The tissues took the stain much better. The edema either had disappeared or was much less evident. The collagenous bundles stained better, were less swollen and were arranged in a more orderly manner. The blood vessels were more distinct, and there was less perivascular edema. The cells of the epidermis were seen to stand out much better after treatment. There were no characteristic changes in the elastic tissues, and cellular infiltration played no part in the recuperative process.

It is evident that all changes which occur in the senile skin are dependent on the edema which is present. While no evident changes are seen in the blood vessels except the perivascular edema and the concomitant haziness of the vascular tissue and cells, one can assume with a fair degree of certainty that there is a vascular dilatation with an increased permeability of the blood vessel wall to produce that amount of fluid exudation into the tissues. Endocrine treatment caused a decided improvement in the edema and also in the general appearance of the cells and tissues of the epidermis and the cutis, producing a more normal picture.

The effect of endocrine substances on diminishing cell permeability was amply demonstrated by Weinstein [4] and also by Sprunt, McDearman and Raper,[5] by the greater size of the area into which india ink diffuses in castrated animals as compared with normal ones and by a definite diminution in the size of that area after injection of estrogen in castrated animals.

Various observers have noticed vascular changes in the skin in cases of sex hormone deficiency. In spite of the fact that a voluminous literature dealing with these endocrine principles has appeared in recent years, the subject is still in its infancy, and there is no complete agreement between investigators as to the size of the blood vessels involved or as to whether it is or is not accompanied by circulatory changes. For example, Edwards, Hamilton, Duntley and Hubert,[6] in their studies of the circulation of the skin of human castrates, found that the arteries are contracted and the veins dilated and that the blood contains a larger amount of reduced hemoglobin, indicating a predominance of venous blood. They were able to counteract this effect by the injection of testosterone.

On the other hand, Reynolds [7] found that when estrogen is injected in the male rabbit, only the smallest vessels in the rabbit's ear become dilated. This is evident from the resultant pinkish color of the skin. There is no increase in the temperature of the skin supplied by these vessels; hence there is no increased rate of flow.

Reynolds and Foster [8] stated that the effect produced on the capillaries by estrogen is not altered by the removal of the nerve supply; hence the effect may be local and due to acetylcholine.

Foerster, Altenburger and Kroll [9] found that sensitivity depends on the condition of the blood vessels, whether they are contracted or dilated. Contraction causes a diminution of sensitivity and dilatation an increase. Since there are many exceptions to these observations, it becomes evident

4. Weinstein, L.: Further Studies on Prophylaxis of Experimental Infection and in Intoxications with Various Hormone Preparations, Yale J. Biol. & Med. **12**:549, 1940.

5. Sprunt, D. H.; McDearman, S., and Raper, J.: Studies on Relationship of Sex Hormones to Infection, J. Exper. Med. **67**:159, 1938.

6. Edwards, E. A.; Hamilton, J. B.; Duntley, S. Q., and Hubert, G.: Cutaneous Vascular Pigmentary Changes in Castrates and Eunuchoid Men, J. Endocrinol. **28**:119, 1941.

7. Reynolds, S. R. M.: Dermovascular Action of Estrogen, the Ovarian Follicle Hormone, J. Invest. Dermat. **4**:17, 1941.

8. Reynolds, S. R. M., and Foster, F. I.: Vascular Action of Estrogens in the Male, J. Pharmacol. & Exper. Therap. **68**:175, 1940.

9. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervenzystem zur Sensibiltät, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:139, 1929.

that the influence on the reactivity of the sensory apparatus does not occur by way of the blood vessels. There must be processes which act directly on the receptors of the nerve fibers. Some may act on the sympathetic and others on the parasympathetic nervous system.

According to Lewis,[10] the red line (dilated blood vessels) caused by stroking the skin is due to injury of the epidermal cells. This causes a conversion of the histidine found in the cells into histamine. This is proved by the fact that when the epidermis is pricked by a needle not deep enough to reach the cutis there is a vascular dilatation.

Similarly, Rothman [11] stated that itching is due to the development of irritating substances within the epidermis. These may cause local inflammatory changes, or they may cause itching by irritating the nerve endings. When the epidermis is removed there is no itching. In spite of these observations he felt that not all itching is caused by histamine-like substances.

Itching dermatoses are frequently accompanied by disturbances in the vegetative nervous balance, notably vagotonia. That is the reason for the favorable influence of epinephrine and atropine on itching. The frequent occurrence of vasomotor reflexes, such as flushing, leads one to believe that the itching and the vasomotor reflexes are intimately related to each other or have a common cause.

From the considerations given here, one can see that with the present state of knowledge of the physiology of itching, not excepting senile pruritus, it is impossible to ascribe it to any one factor in any given case. The probability is that the vegetative nervous system, the hormonal apparatus and the biochemical processes occurring within the cell are mutually interdependent and that there is probably a continuous transformation of one form of energy into another.

## SUMMARY AND COMMENT

To date we have treated 16 patients who were suffering from senile pruritus with estrogens and androgens. In the first 12 uniformly good results were obtained. The other 4 patients, while showing a certain amount of improvement, were not treated long enough for the results obtained to be entirely convincing, although we feel that these patients will in the end show a completely favorable response, as did the others, because their courses are identical. We have employed extremely small doses in treating our patients. The reason for this is that we had no possible guide as to what constitutes an adequate dose, this being the first time generalized senile pruritus has been treated with this type of

10. Lewis, T.: Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

11. Rothman, S.: Physiology of Itching, Physiol. Rev. **21**:357, 1941.

medication. Case 8 is a good example of the difficulties encountered from that source. The treatment was almost given up as a failure after use of the ordinary, small dose, but brilliant results were observed when a 20 mg. pellet of testosterone propionate was injected subcutaneously. It appears that treatment by means of insertion of the pellet offers interesting possibilities. The absorption of the pellet is extremely slow, and there is apparently enough active androgen remaining for a long time to keep the patient free from symptoms. In case 5 the patient became symptomless a short while after insertion of the pellet and has remained so to the time of writing, for eight months. In practically all patients who were treated with the injection method, the itching disappeared after about four weeks of medication with androgen or estrogen. They remained free from itching for a period of two to seven weeks, in most cases for about three weeks. After this the itching invariably returned. From this one can see that the treatment does not cure but supplies a systemic want and is effective only for the duration of the treatment and a short time afterward.

Several considerations impelled us to treat senile pruritus in the female with testosterone propionate and in the male with estrogens. The androgens and estrogens are found in both sexes, only in varying degrees. Their chemical structure is similar, both being steroids, and on occasion they act synergistically. When we started this investigation, we hoped to be able to demonstrate a sameness of action of the androgens and estrogens on senile pruritus of both sexes, but we obtained absolutely no results in the 2 female patients and in 2 of the males. The third male patient is for the present out of our reach. There can be no better proof of the specific action of androgens and estrogens in senile pruritus than that there was an almost immediate response when the treatment was reversed and the female patient was treated with estrogen and the male with androgen.

To guard further against error in estimating the authenticity of the effect of the endocrine substances on senile pruritus, several patients whose itching returned after an intermission in the endocrine medication were given injections of sesame oil and several others 1 per cent solution of procaine hydrochloride. The itching in each case remained stationary or increased in intensity during those injections, which proved that they had no effect on the pruritus. This was an important finding. It established the facts that sesame oil had no hormone action and also that the relief of itching after endocrine medication was not due to psychic influence, since we carefully guarded against the patients' ever suspecting that they received anything but endocrine medication.

No ill effect was noticed from the use of testosterone propionate in the male patient. Female patients were not treated with that drug for a

long enough period to expect any mishaps from it. The same can be said about the treatment of male patients with estrogens. Some of the effects of estrogens on the sex organs of women, however, presented rather a serious problem. One patient's nipples became painful and remained so during the entire course. This complication not being of a serious nature, we decided to disregard it and continued treating her with estradiol dipropionate until she was relieved of her itching. The vaginal bleeding which occurred in 1 patient after several injections of that drug, however, was serious enough to demand attention. At first, we changed the drug to estradiol benzoate, and, while there was a diminution in the amount of bleeding, the itching returned. The same happened when the dose of estradiol dipropionate was diminished by one half. The fact that one of us [12] successfully employed testosterone propionate in the treatment of functional uterine bleeding motivated us to try it in combination with an estrogen. Ten milligrams of testosterone propionate combined with 1 mg. of estradiol dipropionate solved our problem, and our effort was crowned with success. Both the bleeding and the itching disappeared within a comparatively short time.

In case 1, in addition to the itching and its effects on the skin, namely, scratch marks, eczematoid lesions and pigmentation, there were also several small areas of follicular keratosis on the back. When this patient was shown at a meeting of the Bronx Dermatological Society, Dr. Paul Gross suggested that the presence of the mild follicular keratosis might indicate a vitamin deficiency. He suggested vitamin A treatment, believing that equally good results might be obtained with either the endocrine or the vitamin medication. This patient readily responded to the treatment with testosterone propionate, while large doses of vitamin A produced no effect on the pruritus.

This phase of the treatment of pruritus senilis cannot be considered closed, but requires further investigation. This we have recently undertaken, and we hope to report more complete results at a future date. Under investigation are also the metabolism of creatine and creatinine in the aged and in persons suffering from senile pruritus and the influence on it of treatment with estrogens and androgens. The urine voided during twenty-four hours preceding the first course of treatment was collected and tested for its creatine and creatinine content. Unfortunately, some of the urines collected were not available for testing, as it was not always possible to obtain a reliable specimen. In the 5 specimens tested, the creatine content was, respectively: none, 7.7 per cent, 8.7 per cent,

12. Abarbanel, R.: Therapeutic Rationale for the Use of Testosterone Propionate in the Immediate Treatment of Functional Uterine Bleeding, Tr. Am. A. Obstetricians, Gynecologists & Abd. Surgeons **52**:163, 1937.

11 per cent and 15 per cent of the total creatine and creatinine in the urine. One patient who showed no creatine in the urine was fed 1 quart (1,000 cc.) of milk, and his urine was collected during the next twenty-four hours. It was found to contain 185 mg. of creatine. This observation corroborates that of Kun and Peczenik,[13] who stated that the disturbance is not in the internal creatine but that only the assimilation of creatine brought from outside is interfered with.

## CONCLUSIONS

Senile pruritus readily yields to androgen and estrogen medication. From this it may be deduced that the condition is due to a sex hormone deficiency. There are definite histologic changes in the skin which are favorably influenced by this endocrine medication. In senile pruritus androgens and estrogens appear to act specifically in the individual sexes. This treatment of pruritus senilis cannot be regarded as a cure. It is a method of treatment which exerts a maintenance effect on persons with a deficiency of these endocrine factors. The amount of treatment required and the dosage vary with the patient. Ten milligrams of testosterone propionate or 1 mg. of estradiol dipropionate constitutes a safe dose. There is apparently no ill effect from this medication except for the local effect of estrogens on the female sex organs, namely, uterine bleeding and painful nipples. This can be readily counteracted by combining an estrogen with an androgen (testosterone propionate).

The material for this investigation was furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

1955 Grand Concourse.

2 Minerva Place.

Harlem Hospital.

13. Kun, H., and Peczenik, O.: Geschlechtsspezifische Wirkung der Sexualhormone auf den Kreatinstoffwechsel, Arch. f. d. ges. Physiol. **236**:471, 1935.

# INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS

## FOLLOW-UP REPORT ON THE TEN DAY SYRINGE METHOD OF TREATMENT

ARTHUR G. SCHOCH, M.D.
AND
LEE J. ALEXANDER, M.D.
DALLAS, TEXAS

Because we have received numerous inquiries since the publication of our preliminary report [1] on intensive arsenotherapy of early syphilis, we thought it advisable to outline briefly the added experience which we have had with the method.

To date we have treated over 350 patients. Of these, 208 were treated by the ten day syringe method, the technic consisting of giving 120 mg. of mapharsen daily for ten consecutive days (a total of 1,200 mg.) by rapid syringe injection. The remaining 142 patients have been treated with a revised system, consisting of giving smaller individual doses over a longer period of time. It approaches somewhat the original plan [1] by which we treated our first 8 patients.

In the entire group we encountered hemorrhagic encephalitis 3 times: In 1 case it was severe and resulted in death; in the second case it was moderately severe and resulted in recovery, and in the third case the encephalitis was questionable and also resulted in recovery. The third case might more properly be labeled one of prodromal encephalitis, or toxic encephalopathy.

Of the entire group, 103 patients treated by the ten day syringe method have been under close observation from six to eighteen months. In this group we have obtained 77 per cent satisfactory results (the patients became clinically and serologically well). The results in 11 per cent are pending (the patients became clinically well, but they still have residual reagin in the blood at the time of writing). In the remaining 12 per cent the treatment was a failure (3 patients with

From the Dallas Syphilis and Venereal Disease Clinic, Department of Health, Parkland Hospital, and the Southwestern Medical Foundation.

1. Schoch, A., and Alexander, L. J.: Short-Term Intensive Arsenotherapy of Early Syphilis: Preliminary Report, Am. J. Syph., Gonor. & Ven. Dis. **25**:607-609 (Sept.) 1941.

infectious relapses, 1 with periostitis, 6 with serologic relapses and 2 with positive serologic reactions of the spinal fluid).

These results compare favorably with those of the five day continuous intravenous drip method reported by Elliott and his collaborators [2] and by Leifer, Chargin and Hyman.[3]

1719 Pacific Avenue.

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2. Elliott, D. C.; Baehr, G.; Shaffer, L. W.; Usher, G. S., and Lough, S. A.: An Evaluation of the Massive Dose Therapy of Early Syphilis, J. A. M. A. **117**:1160-1166 (Oct. 4) 1941.

3. Leifer, W.; Chargin, L., and Hyman, H. T.: Massive Dose Arsenotherapy of Early Syphilis by Intravenous Drip Method: Recapitulation of the Data (1933 to 1941), J. A. M. A. **117**:1154-1160 (Oct. 4) 1941.

# INCIDENCE OF TUBERCULOSIS OF THE SKIN

EMANUEL GAHAN, M.D.
NEW YORK

Tuberculosis of the skin presents a curious distributional pattern; it is common in Europe and uncommon elsewhere. One encounters only an occasional case in an American dermatologic clinic. No adequate recent estimates are to be found in textbooks or periodicals on dermatology of the frequency of cutaneous tuberculosis in general or of any of the various clinical forms in which it may manifest itself. An attempt is made in this article to determine its frequency in various countries and to compare these statistics with those at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

## GENERAL INCIDENCE IN EUROPE

All recent reports from European dermatologic clinics estimate the frequency of cutaneous tuberculosis as between 1 and 3 per cent of the total number of cases observed. It is noteworthy that climate apparently does not influence its occurrence. From Edinburgh, Scotland, Aitken [1] reported 0.6 to 1 per cent for lupus vulgaris and about 1.25 per cent for tuberculosis of the skin as a whole. Sainz de Aja and Contera [2] gave substantially the same figures for Madrid, Spain: 0.77 per cent for lupus vulgaris. The data given by other authors [3] appear in table 1.

## CLINICAL FORMS

Tuberculosis of the skin may manifest itself in many different forms; it is exceeded in polymorphism only by syphilis. Nevertheless, in about 19 cases of 20 in countries where it is of frequent occurrence, it assumes

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From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital (Dr. George M. MacKee, Director).

1. Aitken, R.: Lupus Vulgaris, Cong. dermat. internat., Budapest **3**:257, 1935.

2. Sainz de Aja, E., and Contera, M. F.: Los lupus (tuberculoso y eritemaosos): Boceto estadistico de 1909 a 1929, Actas dermo-sif. **22**:91-99 (Nov.) 1929.

3. (*a*) Stevanin, M.: Tuberculosi cutanee e tuberculidi (studio statistica), Riv. di pat. e clin. d. tuberc. **14**:304-318 (May 31) 1940. (*b*) Rugh, H.: Ueber die Häufigkeit der Hauttuberkulose, Norsk mag. f. lægevidensk. **9**:847, 1938. (*c*) Collinelli, G.: Statistica delle tuberculosi cutanee, Arch. ital. di dermat., sif. **11**:173-195 (Feb.) 1935. (*d*) Miescher, G.: Haufigkeit der Hauttuberkulose, Cong. dermat. internat., Budapest **3**:292, 1935. (*e*) Albert, W.: Statistische Untersuchungen ueber Hauttuberkulose, Strahlentherapie **32**:309-321, 1929.

one of the six forms listed in table 2.[4] Of the many other clinical aspects of tuberculosis of the skin no one form is present in more than 1 per cent of the total number of cases encountered. Lupus erythematosus and granuloma annulare are excluded from the counts.

TABLE 1.—*Geographic Distribution of Tuberculosis of Skin in Europe*

| | Years | Cutaneous Diseases, New Cases | Tuberculosis of Skin | |
|---|---|---|---|---|
| | | | Cases | Percentage |
| Padua, Italy [3a] | 1919-1938 | 29,538 | 530 | 1.7 |
| Oslo, Norway [3b] | 1927-1937 | 20,878 | 618 | 2.9 |
| Bologna, Italy [3c] | 1896-1932 | 98,520 | 1,419 | 1.4 |
| Zurich, Switzerland [3d] | 1917-1934 | 7,000 per yr. | 150 per yr. | About 2 |
| Freiburg, Germany [3e] | 1915-1928 | 4,000 per yr. | 876 | 1 to 1.5 |

TABLE 2.—*Relative Frequency of Common Clinical Forms of Cutaneous Tuberculosis in Europe*

| | Lupus Vulgaris | Tuberculosis Verrucosa | Papulonecrotic Tuberculid | Scrofuloderma | Erythema Induratum | Sarcoid (Boeck) | Other Forms | Total |
|---|---|---|---|---|---|---|---|---|
| Padua, Italy [3a] | 336 | 47 | 9 | 78 | 29 | 2 | 29 | 530 |
| Oso, Norway [3b] | 303 | 13 | 37 | 95 | 87 | 26 | 7 | 568 |
| Bologna, Italy [3c] | 860 | 37 | 63 | 275 | 70 | 5 | 109 | 1,419 |
| Zurich, Switzerland [3d] | 299 | 26 | 33 | 50 | 55 | 10 | 15 | 488 |
| Freiburg, Germany [3e] | 654 | 42 | 4 | 146 | 15 | 0 | 15 | 876 |
| Madrid, Spain [4a] | 352 | 28 | 30 | 179 | 173 | 0 | 13 | 775 |
| Breda, Netherlands [4b] | 151 | 2 | 25 | 42 | 22 | 0 | 11 | 253 |

TABLE 3.—*Age and Sex Incidence of Lupus Vulgaris in Europe*

| | Total Cases | Men | Women | Age, Years | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Under 10 | 10-20 | 20-30 | 30-40 | 40-50 | 50 and Over |
| Padua, Italy [3a] | 336 | 90 | 246 | 20 | 77 | 70 | 65 | 52 | 46 |
| Oslo, Norway [3b] | 303 | 104 | 199 | 65 | 82 | 50 | 43 | 37 | 25 |
| Bologna, Italy [3c] | 860 | 344 | 516 | 110 | 207 | 133 | 108 | 95 | 107 |
| Zurich, Switzerland [3d] | 299 | 85 | 214 | =* | = | = | = | = | = |
| Freiburg, Germany [3e] | 654 | 232 | 422 | 205 | 200 | 81 | 71 | 48 | 49 |
| Madrid, Spain [4a] | 352 | 130 | 222 | = | = | = | = | = | = |
| Breda, Netherlands [4b] | 151 | 50 | 101 | = | = | = | = | = | = |
| Rotterdam, Netherlands [5a] | 1,785 | 642 | 1,143 | 583 | 567 | 311 | 324† | † | † |

* = indicates that the incidence was not stated.

† Incidence not given for patients in higher decades. Three hundred and twenty-four were over 30 years of age.

In Europe, as will be noted in table 2, lupus vulgaris is by far the most common manifestation of tuberculosis of the skin, being presented

4. (*a*) Covisa, J.: La tuberculose cutanée, Eighth Internat. Dermat. Cong., Copenhagen, 1930, p. 365. (*b*) van Vonno, N. C.: L'Association des affections tuberculeuses de la peau avec celles des autres organes, Ann. de dermat. et syph. **2**:543, 1931. (*c*) Footnote 3.

in about two thirds of all the cases.[5] It is seen twice as often in women as in men, and in at least half of the cases it begins before the age of 20. Scrofuloderma is the second most common form of cutaneous tuberculosis in Europe, occurring in from 10 to 15 per cent of the cases. It is seen as often in men as in women. Like lupus vulgaris, it usually begins before the age of 20. Erythema induratum is third in frequency and is found in about one tenth of the total number of cases. It is at least four times as common in women as in men. Like most other forms, it usually occurs in young persons. Tuberculosis verrucosa is present in about 5 per cent of the total number of cases of tuberculosis of the skin. It is the only variety which is more common in men (in whom it is seen at least three times as frequently as in women) and in adults. Papulonecrotic tuberculid is present in from 2 to 5 per cent of all cases. Its incidence is higher in women and in persons below the age of 20.

### INCIDENCE IN THE UNITED STATES

At the Skin and Cancer Unit approximately 1 new patient in 1,500 has tuberculosis of the skin. During the past five years approximately 150,000 new patients have been admitted, of whom 100 had tuberculous lesions of the skin. Lupus vulgaris is the most common form, but it occurs in only 43 per cent of the total cases, and most of the patients are adults. This is probably because most of these patients are foreign born and have the disease when they come to this country. Of the other forms, not more than 2 or 3 cases of any one variety are encountered in a year. It is not possible, therefore, to establish any rule of frequency for their occurrence. Table 4 shows the incidence of the more common forms of tuberculosis of the skin at the Skin and Cancer Unit over the past five years.

For other parts of the United States no recent statistics are available.

In the far South the concensus is that tuberculosis of the skin is virtually nonexistent.[6] Kirby-Smith,[7] for example, stated that in twenty-six years of practice in Florida he encountered not more than 20 cases. It is particularly interesting to note that in each of the few cases which are encountered the condition is of hematogenous origin; the localized or primary varieties, such as lupus vulgaris or tuberculosis verrucosa, are unknown.

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5. (*a*) Kleipool, C. M.: Die Frage der Hauttuberkulose in Holland, Cong. dermat. internat., Budapest **3**:281, 1935. (*b*) Footnote 4.

6. French, E. D., and Lefholz, R.: Lupus Vulgaris in the Far South, South. M. J. **30**:270 (March) 1937.

7. Kirby-Smith, in discussion on French and Lefholz.[6]

## INCIDENCE ELSEWHERE

In South America cutaneous tuberculosis has about the same geographic distribution as in the United States. It is rare in the temperate climates and particularly rare in tropical regions. The incidence of lupus vulgaris in South America is also similar to that in the United States. In Uruguay and in Argentina lupus vulgaris, although constituting the most important single form of tuberculosis of the skin, is responsible for less than half of the total number of cases; in Brazil there have been only 5 or 6 cases over a score of years.[8]

From Australia, which is a warm country and inhabited by the white race, Molesworth,[9] of Sydney, said that lupus vulgaris is almost unheard of and that he could recall encountering in Australia only 4 or 5 cases of papulonecrotic tuberculid, about 20 cases of lichen scrofulosorum,

TABLE 4.—*Incidence of Common Clinical Forms of Cutaneous Tuberculosis at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital*

| Year | Lupus Vulgaris | Erythema Induratum | Sarcoid (Boeck and Darier-Roussy) | Tuberculosis Verrucosa | Rosacea-Like Tuberculid of Lewandowsky: Scrofuloderma | Rosacea-Like Tuberculid of Lewandowsky: Other Forms | Total |
|---|---|---|---|---|---|---|---|
| 1936 | 9 | 3 | 3 | 1 | 1 | 3 | 23 |
| 1937 | 9 | 2 | 1 | 1 | 0 | 3 | 19 |
| 1938 | 10 | 0 | 1 | 2 | 1 | 1 | 18 |
| 1939 | 6 | 3 | 5 | 0 | 1 | 1 | 21 |
| 1940 | 9 | 3 | 1 | 0 | 1 | 3 | 19 |
| Total | 43 | 11 | 11 | 4 | 4 | 11 | 100 |

about 10 cases of erythema induratum, 1 case of Boeck's sarcoid, 2 cases of lupus pernio and none of Darier-Roussy sarcoid. There is no dearth of clinical material in Sydney, which, with its 1,300,000 inhabitants, is the second largest city in the British Empire.

## SUMMARY

Tuberculosis of the skin is apparently endemic in Europe, where climate is not a factor in its frequency. It appears to be as common, or almost as common, in Spain and Italy as it is in Norway and Scotland. In all other countries climate is a factor in its incidence; it is rare in temperate regions, and it is almost nonexistent in warm regions.

8. Rabello, E.: La fréquence de la tuberculose cutanée dans l'Amérique du Sud, Eighth Internat. Dermat. Cong., Copenhagen, 1930, p. 380.

9. Molesworth, E. H.: Is Lupus Erythematosus a Tuberculide? Effect of Climate upon Lupus Erythematosus, Tuberculides, and Skin Tuberculosis, Urol. & Cutan. Rev. **37**:629 (Sept.) 1933.

The most important manifestation of the disease in Europe is lupus vulgaris, which accounts for about two thirds of the cases. Scrofuloderma, erythema induratum, tuberculosis verrucosa and papulonecrotic tuberculid follow in the order named. These five forms account for at least 90 per cent of the total number of cases.

In tropical regions in almost all of the few cases that are encountered the condition is of hematogenous origin.

## COMMENT

The distributional pattern of tuberculosis of the skin is different from that of lupus erythematosus. This speaks, perhaps, against the tuberculous nature of the latter dermatosis. If lupus erythematosus is a tuberculid it is the only one which is as common in the United States (including the far South) and in tropical countries inhabited by the white race as it is in Europe.[10]

12 West Forty-Fourth Street.

10. Gahan, E.: The Geographic Distribution of Lupus Erythematosus, Arch. Dermat. & Syph. **45**:1133 (June) 1942.

# CONGENITAL SYPHILIS ACQUIRED BY FETUS BEFORE APPEARANCE OF CHANCRE IN MOTHER

WILLIAM BICKERS, M.D.
RICHMOND, VA.

It is a matter of some dispute as to when Spirochaeta pallida enters the general circulation after the original inoculation. Formerly, it was taught that this widespread diffusion of the organisms occurred just prior to the appearance of the secondary lesions. This is now known to be not necessarily true. The case herein reported is interesting from several points of view. More specifically, it indicates that the spirochete may enter the general circulation some time before the appearance of the primary lesion.

## REPORT OF A CASE

Doris, aged 17, unmarried, was admitted to the Evangeline Booth Hospital in Richmond, Va., on April 17, 1941. The patient was thirty-eight weeks pregnant by her history, and this was confirmed by the size of the uterus, which measured 34 cm. from the symphysis to the top of the fundus. The fetus lay in the left occipitoanterior position, and the fetal heart rate was 142 per minute in the left lower quadrant. The general physical examination showed no abnormalties, and the patient stated that her pregnancy had been uneventful. She had received no prenatal care except a Wassermann test, made on April 2, the reaction to which was reported as negative. She stated that she had never had any genital lesion or eruption of any type. Fortunately for the purpose of this report, the patient had applied for a position on July 8, 1940, at which time the Wassermann reaction of the blood was reported as negative.

The patient admitted having had sexual intercourse on April 15, two days before her admission to the hospital, with a man who was traced with considerable difficulty. Personal interview with this sexual partner established that he had had a primary sore nine weeks before contact with the patient, the nature of which was confirmed by a positive Wassermann reaction of the blood. He had received no treatment for syphilis. The Wassermann test of the blood was repeated as a routine on my patient on her admission to the hospital, April 17, and the reaction was negative.

A complete examination at this time revealed no adenopathy; the external genitals were normal, and there was no local lesion of any kind and no leukorrhea. On May 3 the patient went into spontaneous labor, and after nine hours low forceps delivery was made, with a mediolateral episiotomy.

The postpartum course was normal until the third day, when the temperature went to 103 F. and a profuse foul discharge from the vagina was noted. Examination at this time revealed a shallow dirty ulcer about 1 cm. in diameter on the left labium minus. The ulcer was nontender; there was no induration, and

the lesion was the penetrating, excavating type suggesting chancroid. A dark field examination on this day did not show S. pallida, but this smear was taken by the nurse. On the following day a smear revealed typical S. pallida. The Wassermann reaction on this, the fourth day post partum, was negative. An intravenous injection of mapharsen, 0.06 Gm., was given and repeated two days later. In the meantime the episiotomy wound became infected, the sutures broke down and the wound opened. One week after the first mapharsen treatment the ulcer was clean and beginning to epithelize. The Wassermann reaction on May 18, fifteen days after the ulcer was first noted, was reported positive. This was confirmed. A typical secondary macular-papular rash appeared three weeks after the appearance of the ulcer.

The male infant weighed 6 pounds and 4 ounces (2,835 Gm.), and careful examination immediately after birth revealed no stigmas suggestive of congenital syphilis. The Wassermann reaction on the fourth day, immediately after S. pallida was discovered in the mother, was reported negative. Examination of the baby at 3 weeks of age revealed quite another picture. The characteristic perianal fissures and the small fissures about the angles of the mouth plus the scaling of the epidermis on the palms and soles left little doubt as to the diagnosis. The Wassermann reaction at this time was positive. The baby had congenital syphilis.

## COMMENT

This case is remarkable in that it is a proved one of congenital syphilis in a newborn child acquired from the mother before the appearance of the primary sore in the mother. It will be suggested that the patient had a "chancre redux" and that the syphilis was present long before the appearance of the ulcer which I assume to be the primary lesion. This contingency has been eliminated, I think, by the fact that a negative Wassermann reaction in the patient is known to have been present ten months, one month and two weeks before the appearance of the chancre. Furthermore, a history of contact with an infected partner has been established twenty-two days before the appearance of the primary sore. And last, and perhaps most important, the secondary rash appeared in the mother five weeks after the initial lesion.

807 West Franklin Street.

# Clinical Notes

## ALOPECIA TOTALIS IN FATHER AND DAUGHTER

### Report of Cases

JOSEPH M. SHELTON, M.D., WASHINGTON, PA., AND LESTER HOLLANDER, M.D., PITTSBURGH

Cockayne[1] stated in 1933 that the tendency toward loss of hair is closely linked to the genes for dark hair. He cited Sabouraud as having reported a familial history of loss of hair in 22 of 81 cases of alopecia areata. We think that the cases here reported furnish evidence of a hereditary tendency toward complete loss of hair on the scalp and body.

#### REPORT OF CASES

CASE 1.—Mrs. M. S., a white woman aged 32, was seen by us on Oct. 15, 1941 because of a complete loss of hair of the entire body. It had begun in March 1941 as a typical alopecia areata involving the left parietal region of the scalp. This spread rapidly and involved the entire scalp, eyebrows, axillas, pubes and extremities. She had been under treatment with ultraviolet irradiation and application of phenol without success for three and one-half months before we first saw her.

On examination she presented complete loss of hair. The scalp and other involved areas appeared to be smooth and of normal color and texture.

General physical examination showed nothing else abnormal. Reactions to serologic tests for syphilis were negative. A complete blood count showed no abnormality. Her basal metabolic rate was + 14 per cent; however, she had recently taken small doses of thyroid. A complete dental survey and dental roentgenograms showed no apical infections or evidence of impaction. She had a number of silver amalgam fillings, all apparently in good condition. A roentgenogram of the sella turcica showed no evidence of pituitary abnormality.

The patient stated that her father had had "some trouble" with his hair early in his life, that being her chief reason for feeling apprehensive about her own condition. On further questioning it was found that his hair had been lost completely and had never regrown to any extent. She was asked to bring her father in for examination, which she did. He proved to be most uncooperative, and we were able to obtain only a brief history and to make a most superficial examination.

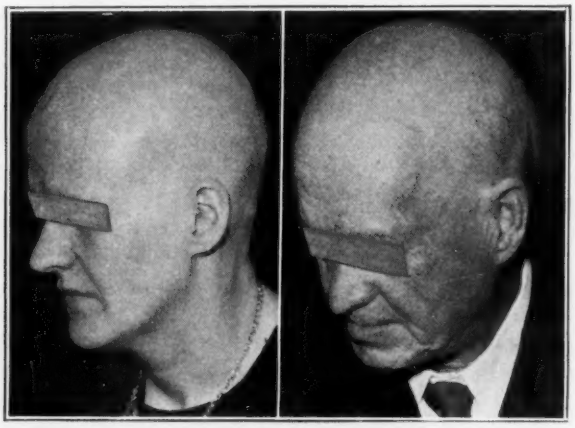
CASE 2.—C. H., the father, white, aged 62, had a patch of alopecia the size of a half-dollar on the right side of his scalp which developed when he was

From the Pittsburgh Skin and Cancer Foundation.

1. Cockayne, E. A.: Inherited Abnormalities of the Skin, London, Oxford University Press, 1933, p. 353.

15 years of age. During the following two years his hair fell out completely, including that of the entire body. There has never been any noteworthy regrowth except a few hairs at the sides of the scalp and an occasional transient fuzz on the eyebrows and in the axillas.

On examination a few straggling hairs were noted at the sides of the scalp. Otherwise, he was completely hairless. The involved areas of skin appeared to be otherwise normal. He stated that his general health had always been good and could offer no suggestions as to the cause of his alopecia. His father and mother died at 81 and 67 years of age respectively, both with good heads of hair. One brother and one sister had died at 65 years of age. His brother had five children and his sister two children, none of whom have evidenced any loss of hair. As far as he knew, his wife's (our patient's mother) family had never shown any similar anomaly.



Father and daughter with alopecia totalis. Note the physical resemblance.

COMMENT

Although in a large percentage of cases of alopecia the condition is regarded as being hereditary in origin, total alopecia, as evidenced in this father and daughter, has not been frequently described. The physical resemblance, which is easily discernible in the accompanying illustration, would tend to make the hereditary angle of this total alopecia more plausible. It is true that the loss of hair began at the age of 15 in the father while in the daughter it appeared much later in life. It is also true that the pattern of hair loss was not completely identical in these cases. Both of these dissimilarities are important from a genetic point of view, but this importance is difficult for us to evaluate. We are simply reporting this case as a dermatologic curiosity and as additional evidence of the hereditary background of alopecia in some cases.

933 Washington Trust Bulding, Washington, Pa.
631 Jenkins Building, Pittsburgh.

# MOLLUSCUM CONTAGIOSUM CURED WITH SULFAPYRIDINE

WILLIAM R. HILL, M.D., AND JOHN G. DOWNING, M.D., BOSTON

The paucity of reports on the successful treatment of virus diseases with sulfanilamide and its derivatives justifies the recording of clinical impressions gained from their employment in cases of this group of diseases.

Schnitker[1] stated that lymphogranuloma venereum was the only virus infection which responded to these drugs.

In a recent article Sommerville[2] wrote that molluscum contagiosum, a virus disease limited strictly to the skin, was cured by the oral use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). He reported 8 cases, with clinical cures in 6. Two patients experienced early toxic reactions, discontinued treatment and lapsed from observation. Of the 6 cured patients, 4 who took the sulfanilamide compound regularly were cured at varying periods, ranging from two to eight weeks. Three to four months elapsed, however, before final cure was effected in the 2 persons who used the drug at irregular intervals. The effective daily dose of the drug varied from a minimum of 30 grains to a maximum of 60 grains (2 to 4 Gm.). Dosage appeared to be important, since 2 patients who failed to respond when the initial daily dose was 15 grains (1 Gm.) did so when this was increased to 30 grains. Unfortunately, the level of concentration of the drug in the blood was not determined. Five of the 6 patients in Sommerville's series were children, the youngest 9 months of age and the oldest 15 years.

To this report we wish to add a case of molluscum contagiosum cured with sulfapyridine.

## REPORT OF A CASE

H. F., a white man aged 44, was examined on Dec. 1, 1941. He complained of nonpruritic lesions of one year's duration, which began on his trunk and subsequently involved his arms. Twice a week after a workout in a gymnasium he had been accustomed to receive massage, and he thought that the lesions had been spread by the masseur.

Examination revealed fifteen translucent globular papules 0.5 cm. in diameter scattered over the anterior and lateral parts of the chest, the upper part of the abdomen and the arms. Umbilication was seen at the summit of the papules. Several lesions on the abdomen were secondarily infected. Two lesions on the right forearm had hemorrhagic puncta in the umbilicated core. We did not examine microscopically for molluscum bodies the expressed content of the papules or a specimen removed for biopsy; however, we feel that the clinical picture left no doubt as to the diagnosis.

The patient was instructed to take 1 tablet of sulfapyridine orally four times a day. He returned one week later, on December 6, stating that he had taken 25 tablets (total amount, 12.5 Gm.). At this examination all but one of the lesions had disappeared. This lesion was desiccated with the monopolar current.

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1. Schnitker, A.: Sulfanilamide, Sulfapyridine and Allied Compounds in Infections, New York, Oxford University Press, 1940, p. 29.

2. Sommerville, J.: Molluscum Contagiosum and M. & B. 693, Brit. J. Dermat. **53**:255-257 (Aug.-Sept.) 1941.

Since the incubation period had been reported to be as long as ten weeks, we communicated with our patient on March 30, 1942, sixteen weeks after the disappearance of the last lesion. He had remained clinically cured.

### COMMENT

Older methods of treating molluscum contagiosum, such as curettage, extraction and desiccation, have been tedious and time consuming. Children have been reluctant to accept treatment because of pain incidental to the use of destructive methods. The lesions occasionally become secondarily infected. Oral administration of sulfanilamide or one of its derivatives appears to be the ideal therapeutic approach to this persistent and contagious virus disease of the skin.

520 Commonwealth Avenue.

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## CONTACT DERMATITIS DUE TO COD LIVER OIL

### Report of a Case

ELLIS P. COPE, M.D., LITTLE ROCK, ARK.

Preparations of cod liver oil have been in use for a number of years as topical remedies in the treatment of chronic ulcers of various types. To the best of my knowledge, no case of true allergic dermatitis of contact type has ever been attributed to the cod liver oil itself in any of these preparations.

### REPORT OF CASE

Mr. P., aged 37, a meat slicer in a quick lunch restaurant, had varicose veins about eight years ago. The saphenous vein was ligated, and smaller veins were injected, with good sclerosing effects. (His physician at that time has since died, and the sclerosing agent used is not known.)

In July 1941 an ulcer developed on the lateral surface of the lower third of the right leg. He treated this ulcer with wet compresses of potassium permanganate and an elastic bandage. Healing was complete in about three weeks. In early December the ulcer recurred; but it did not respond to the previous treatment, and he was advised to use an ointment containing a cod liver oil concentrate. This ointment was purchased in 1 ounce (30 Gm.) tubes, and its use was attended by gradual healing of the ulcer. On Jan. 10, 1942 he began buying the same ointment in ½ pound (187 Gm.) jars (white porcelain), which were filled from a large container by the pharmacist. Ten days after he began using the ointment in bulk, an acute dermatitis appeared. The patient treated the increasing area of dermatitis with ever wider applications of the ointment.

On February 7, when the patient was first seen by me, there was an acute vesicular dermatitis of the entire right leg, with three shallow ulcers the size of a half dollar on the lower third of the leg. The femoral glands were swollen, and the temperature was 101 F. Removal of the ointment and elevation of the extremity with continuous wet dressings caused rapid improvement of the dermatitis. There was generalized itching, and a few scattered eczematous areas appeared on the other extremities and on the trunk for a few days.

The patient was given a patch test in the usual manner with the ointment from his own jar. In thirty-six hours there was a bullous reaction at the test site

with a slight recurrence of generalized itching. He was then given patch tests with petrolatum, hydrous wool fat, cholesterolized petrolatum and a liquid cod liver oil concentrate (for oral use) made by the manufacturer of the ointment. In forty-eight hours he showed a positive (2 plus) reaction to the concentrate and negative reactions to the other test substances.

Correspondence with the manufacturer elicited the information that the ointment contains yellow wax and essential oils in addition to the cod liver oil and some of the other ingredients tested. However, the liquid cod liver oil concentrate contains nothing but fish liver oil derived from a number of species; no preservatives, essential oils or other chemicals are added. It is the same oil used in the ointment. It therefore appears that this case is one of true allergic hypersensitivity to contact with cod liver oil.

703 Donaghey Building.

## NAIL POLISH DERMATITIS IN A MAN

WILLIAM GARBE, M.D., TORONTO, CANADA

There have been a great number of reports of nail polish dermatitis in the past year, indicating that some new product or products are being used in the manufacture of this substance. Among 15 of my private patients with this condition one is a man.

### REPORT OF A CASE

C. R., a man aged 63, was referred by Dr. M. K. Bochner. He complained of having a severe eruption about the face, for which he had been hospitalized for seven weeks. While he was in the hospital it was found that he was suffering from diabetes, which could be controlled by diet. He stated that the eruption began behind the right ear and was accompanied by weeping. This area cleared, and then the eyelids and cheeks became involved. The attack resolved gradually. Then in about two weeks the ears, eyelids, nostrils, neck and chest became affected. After close questioning the patient was able to state that the recurrences occurred about every two weeks, including the time he was in the hospital.

On examination the ears, eyelids, cheeks, neck and chest were found to be edematous, especially the eyelids. The eruption was bright red, and the surface was scaly. The nares were fissured and eczematous. The patient complained bitterly of the intense pruritus. During the examination it was noted that he was wearing transparent nail polish. On more pointed questioning with regard to this item he recalled that the exacerbations recurred about the day after he was visited by a barber and manicurist. He was given patch tests with a set of routine substances plus nail polishes. Mild reactions were elicited by two brands of nail polish and a strong reaction was elicited by a third brand. The site of the last-mentioned positive reaction was also tender. He also showed mild reactions to turpentine and to pyrethrum. Patch tests with his personal shaving and toilet substances all gave negative results.

The idea that nail polish caused the rash appealed so strongly to the patient that he had a manicure to prove this to himself. The next day all the hitherto

affected parts flared up as they had previously and the eruption was more extensive than ever.

The patient had a habit of fondling his ears while talking, and he also picked his nose. This would explain the fissuring of the nostrils and the involvement of the ears.

After removal of the nail polish the eruption improved quickly with zinc oxide ointment and silver nitrate compresses. The eruption gradually faded, with several minor exacerbations on the chest; the skin was clear about two weeks later and remained so.

329 Bloor Street West.

# News and Comment

## AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

At the recent meeting of the American Board of Dermatology and Syphilology held in New York, Dec. 12 and 13, 1941, 69 candidates were considered. Fifty-four candidates were awarded the certificate of the board, while 15 candidates did not qualify. Including the diplomates certified at this meeting, there have been 607 physicians certified by this board. Since the board has been in operation, 720 applications have been received.

The survey of graduate training in dermatology and syphilology has been practically completed. The questionnaires of all the institutions with graduates in training for this specialty have been reviewed, and only a few questionnaires now remain to be considered by the board and the Council on Medical Education and Hospitals of the American Medical Association.

The matter of preceptors for graduate students in training has been considered during the past year, and blanks for applicants to act as preceptors for students in training in dermatology and syphilology have been prepared and are ready for distribution.

It has been decided to obtain annual reports of all students in training from chiefs of clinics so that such reports will be available when the applications of these students are considered for certification by the board.

During the past year the board has participated actively with the Committee on Medical Preparedness of the American Medical Association in a survey of physicians throughout the country.

The Syllabus on Graduate Training has been reviewed, and a new issue of this booklet is now being considered.

A complete list of the diplomates of the board, including those certified at the recent meeting, appears in the new edition of the Directory of Medical Specialists, which was published in April. This contains some 4,000 new names of the diplomates of the boards and will supplant the former Registry. The directory can be obtained from the Columbia University Press of New York.

The board decided at the recent meeting that in order to qualify for the oral examination all candidates in group B must previously have passed the written examination.

## DERMATOSES INVESTIGATIONS SECTION

The United States Public Health Service will give a course in occupational dermatoses stressing the war industries during the latter part of July or August. The course will consist of six days of lectures, four hours daily, and six days of visits to at least six plants which manufacture war materials. Applicants for the course should send their names to Dr. Louis Schwartz, Medical Director, Dermatoses Investigations Section, National Institute of Health, Bethesda, Md., before July 15.

# Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

THE LOCAL TREATMENT OF PYOGENIC CUTANEOUS INFECTIONS WITH SULFATHIAZOLE IN AN EMULSION BASE. DONALD M. PILLSBURY, VIRGANE SCHIRER WAMMOCK, CLARENCE S. LIVINGOOD and ANNA C. NICHOLS, Am. J. M. Sc. **202**:808 (Dec.) 1941.

The authors review the results in 190 cases of various dermatoses in which sulfathiazole was applied locally in ointment form. In 134 it seemed probable that pyococci were solely or partially responsible for the eruption. Sulfathiazole in an oil in water emulsion vehicle was effective in the treatment of primary superficial infection of the skin, including staphylococcic or streptococcic impetigo, infectious eczematoid dermatitis, Bockhardt's follicular impetigo and superficial ecthyma. It was equally effective in acute secondary infection of various dermatoses. An oil in water emulsion was found to be the most effective vehicle of application. There was no evidence of absorption of sulfathiazole and no local or general toxic reactions.

THE CAUSATIVE RELATIONSHIP OF DERMATOPHYTOSIS TO THROMBOANGIITIS OBLITERANS. MEYER NAIDE, Am. J. M. Sc. **202**:822 (Dec.) 1941.

Naide points out that dermatophytosis is present in many patients with peripheral arterial disease but it has always been looked on merely as a complication which must be treated to avoid ulceration and gangrene. He emphasizes the possible etiologic significance of the flare-up of dermatophytosis which precedes attacks of migratory phlebitis and arteritis in some patients. Of 10 patients observed during such attacks, 7 had a preceding exacerbation of their dermatomycosis. Thirty patients with thromboangiitis obliterans were examined. Ninety-three per cent had clinical evidence of dermatomycosis; 80 per cent gave positive reaction to the trichophytin test. Of 20 men of similar age but without thromboangiitis obliterans, only 37 per cent had clinical dermatomycosis and 20 per cent gave positive reactions.

Though there is only inconclusive evidence of a causal relationship, Naide states that one should look for and treat persistently any evidence of dermatophytosis in a patient with thromboangiitis obliterans.

NOTE ON LOCALIZED LIPOID ATROPHY IN DIABETES. ZOLTON T. WIRTSCHAFTER and EDWARD D. SCHWARTZ, Am. J. M. Sc. **202**:880 (Dec.) 1941.

The cause of localized lipoid atrophy at the site of injections of insulin in diabetic patients has remained obscure in spite of numerous theories proposed by various authors who have reported instances of it. Usually it is suggested that the patient change the site of injection and when he does so the condition improves. Wirtschafter and Schwartz report an instance in which recovery took place without variation of the site of injection. They believe that some intrinsic factor makes certain patients susceptible to this condition and that when this factor is eliminated spontaneous recovery occurs.

LYNCH, St. Paul.

A CASE OF CORNEAL ULCER ASSOCIATED WITH LYMPHOGRANULOMA VENEREUM. G. P. MEYER and J. REBER, Am. J. Ophth. **24**:161 (Feb.) 1941.

Meyer and Reber report a case of corneal ulcer in a 29 year old Negro woman referred by the proctologic department, where a diagnosis of venereal lymphogranuloma had been made. Despite treatment the ulcer progressed. The Frei reaction was then found to be positive, and with the use of sulfanilamide the ulcer healed completely in two weeks.

W. S. REESE. [ARCH. OPHTH.]

BIOLOGIC FALSE POSITIVE SEROLOGIC REACTIONS IN TESTS FOR SYPHILIS. CHARLES F. MOHR, JOSEPH EARLE MOORE and HARRY EAGLE, Arch. Int. Med. **68**:1161 (Dec.) 1941.

Eleven cases in which positive serologic reactions occurred in patients with diseases other than syphilis were selected from a series of approximately 200 such cases observed during the past fifteen years. The conditions reported are a subacute infection of unknown cause, acute labyrinthitis of unknown cause, vaccinia, pneumonia, sore throat of unknown cause, infectious mononucleosis and rat bite fever. A low titer was revealed in most of these cases, but in 2 instances it was as high as is usual in early stages of syphilis. The necessity for caution in the interpretation of serologic reactions is again emphasized by the authors.

LYNCH, St. Paul.

KERATOSIS DIFFUSA FOETALIS (REPORT OF CASE). JOHN JUDD SHIELDS and JAMES E. BOWMAN, Arch. Pediat. **57**:756 (Dec.) 1940.

A girl showed no abnormalities at birth except cutaneous lesions, which were somewhat suggestive of sclerema. The skin became dry and exfoliation became a dominant feature; so the diagnosis of dermatitis exfoliativa neonatorum was made. Though the definite microscopic changes characteristic of severe ichthyosis were absent or present to only a slight degree, the diagnosis of keratosis diffusa foetalis was made on the basis of the following observations:

1. The cutaneous lesions were present at birth and appeared to be regressive rather than spreading.

2. There was no spreading erythema preceding exfoliation, such as is described in cases of Ritter's disease.

3. The skin was thickened into parchment-like sheets, in contrast to the peeling of normal-appearing skin which occurs in Ritter's disease.

4. There were no blebs and no Nikolsky sign (a looseness of the outer cutaneous layers on rubbing).

5. Ectopian deformity of the external ears and clubbing of the fingers and toes were present.

The patient lived for three and one-half days.

The observations at autopsy are presented.

ORR, Buffalo. [AM. J. DIS. CHILD.]

SCLERODERMA WITH PULMONARY FIBROSIS. J. R. MURPHY, P. KRAININ and M. J. GERSON, J. A. M. A. **116**:499 (Feb. 8) 1941.

Murphy, Krainin and Gerson report the case of a 30 year old Negress, a housewife, with scleroderma who also complained of difficulty in breathing because of a sensation of tightness in the chest. A roentgenogram of the chest revealed a diffuse network-like shadow extending from the cardiac border to the periphery of the pulmonary fields. An induced pneumothorax demonstrated that these pathologic changes were not in the soft tissues of the chest wall. Tuberculosis and bronchiectasis were excluded in the differential diagnosis. The authors believe the pulmonary findings of their case to be unique, the first time that the fibrotic changes in the lungs have been described ante mortem and roentgenographically.

SODIUM PERBORATE OINTMENT AND POISON IVY DERMATITIS. B. SHELMIRE, J. A. M. A. **116**:681 (Feb. 22) 1941.

Shelmire reports experiments showing that oxidation of the poison ivy sap does not decrease its sensitizing propensities. For this reason the advocacy of an oxidizing ointment, such as one containing 10 per cent sodium perborate, is theoretically unsound. Shelmire also found that in practice such an ointment was not superior to zinc oxide ointment and that any protection afforded could be explained on a mechanical basis.

EXFOLIATIVE DERMATITIS AND DEATH DUE TO PHENOBARBITAL. D. L. SEXTON, G. M. PIKE and A. Nielson, J. A. M. A. **116**:700 (Feb. 22) 1941.

Sexton, Pike and Nielson believe that the danger of harmful sequelae from phenobarbital is not fully appreciated. Their patient, a white man aged 39, with a peptic ulcer, received 21 grains (1.36 Gm.) of soluble phenobarbital by mouth over a period of thirteen days. He then became ill with fever, prostration, sore throat, excessive lacrimation, injected conjunctivas and an eruption which became generalized. The rash consisted of erythematous macules with profuse scaling. Death occurred three days after the eruption was first noticed. At autopsy, pleural effusion and pneumonitis were found.

CUTANEOUS AND CONJUNCTIVAL MANIFESTATIONS OF SULFATHIAZOLE INTOXICATION. I. F. VOLINI, R. O. LEVITT and H. B. O'NEIL, J. A. M. A. **116**:938 (March 8) 1941.

Volini, Levitt and O'Neil noted eruptions in 7 of 180 patients who received sulfathiazole, an incidence of 3.8 per cent. The average dose of sulfathiazole for the whole series was 26 Gm., and for those who had cutaneous reactions, 34 Gm. One rash was urticarial, 3 were maculopapular and 3 were nodular, 1 of the last mentioned also being purpuric. Attention is called to the distinctive appearance of the nodular eruption. There was no apparent correlation between the level of the drug in the blood and the development of the rash. Conjunctivitis is a common accompaniment of a cutaneous reaction to the drug. Three of the 7 patients described died, but the cause of death was not determined. The ages of these patients were 69, 56 and 64.

DERMATITIS DUE TO DEXTRINS USED AS AN ADHESIVE ON TAX STAMPS. J. D. WALTERS and E. C. STERN, J. A. M. A. **116**:1518 (April 5) 1941.

Walters and Stern report 2 instances of cutaneous sensitivity to dextrin in female workers who were employed to affix tax stamps and who thus came into prolonged contact with the material in solution. The dextrin is a component of the adhesive surface of tax stamps, as well as of United States postage stamps.

INTERTRIGO (CHAFING) TREATED WITH TANNIC ACID AND BRILLIANT GREEN. L. TULIPAN, J. A. M. A. **116**:1518 (April 5) 1941.

Tulipan has had good results in the treatment of simple intertrigo by the use of a 5 per cent solution of tannic acid sprayed on with an atomizer once or twice daily. If any secondary infection is present a 2 per cent solution of brilliant green (tetraethyldiaminotriphenylmethane sulfate) is sprayed over the tannic acid layer or used in combination with it.

COCCIDIOIDOMYCOSIS. O. J. FARNESS, J. A. M. A. **116**:1749 (April 19) 1941.

Farness reports 5 cases of coccidioidomycosis originating in Tucson, Ariz. In 3 instances there was a fatal outcome. Of 141 Indian school children in an Arizona reservation, 127 (90.1 per cent) reacted to a test dose of coccidioidin. Thirty per cent of the patients in a general hospital reacted to similar tests. Farness believes the dry climate of Arizona favors the dissemination of the disease and, because of the high percentage of persons reacting to the coccidioidin test, that a considerable nidus of the disease is present.

ALOPECIA AREATA: AN APPRAISAL OF ENDOCRINE FACTORS IN ITS CAUSATION. M. WAISMAN and E. J. KEPLER, J. A. M. A. **116**:2004 (May 3) 1941.

Waisman and Kepler believe that although changes in growth and distribution of hair occur frequently among patients who are afflicted with diseases of the endocrine glands, the presence of universal alopecia is not associated with demonstrable changes of the internal secretions. There were no constant changes in the endo-

crine glands of 138 patients with universal alopecia, whose case histories the authors reviewed. In only 4 cases was there a presumably permanent regrowth of hair after two to ten years of the disease.

PEMPHIGUS VULGARIS: FAILURE OF TREATMENT WITH RIBOFLAVIN AND SMALLPOX VACCINE. S. WOLF and G. M. LEWIS, J. A. M. A. **116**:2017 (May 3) 1941.

Negative results following the use of riboflavin (contrary to other reports) and of smallpox vaccine (an original scheme) in the treatment of a patient with pemphigus were reported by Wolf and Lewis. The autopsy did not reveal any lesions in the central nervous system or in the adrenals. There was an acute splenic tumor with focal areas of necrosis, fatty degeneration of the liver and of the heart, bronchopneumonia, acute bronchitis and hydrothorax.

STOMATITIS VENENATA AND DERMATITIS OF THE ANAL ORIFICE FROM CHEWING POISON IVY LEAVES (RHUS TOXICODENDRON). S. H. SILVERS, J. A. M. A. **116**:2257 (May 17) 1941.

A woman aged 38 with a known sensitivity to poison ivy chewed poison ivy leaves on the advice of a physician and of friends. Besides a dermatitis of various surfaces there was a painful stomatitis and an eruption around the anal orifice suggesting that the allergens traversed the gastrointestinal tract unchanged. Silvers warns against attempting desensitization by chewing the leaves, both because of possible untoward reactions and because the dosage cannot be controlled.

OCCUPATIONAL DERMATITIS DUE TO PARACHLORMETACRESOL. W. H. GUY and F. M. JACOB, J. A. M. A. **116**:2258 (May 17) 1941.

Guy and Jacob observed 12 cases of a vesicular dermatitis of the left hands of girls employed in labeling and capping whisky bottles. They found that this was due to contact with a 1 to 1.5 per cent solution of parachlorometacresol. Washing the caps in water before they were handled prevented new cases.

LEWIS, New York.

THE EFFECT OF CITRUS JUICES AND VARIOUS MOUTH PROPHYLAXES ON THE ORAL FLORA AND SALIVA. H. J. FLORESTANO, MYRON A. ELLIOTT and J. E. FABER JR., J. Bact. **41**:605 (May) 1941.

This is a most interesting study in that it was shown that the most effective agents in actual removal of micro-organisms from the mouth were two commercial dentifrices, one containing sodium ricinoleate and the other sodium alkyl sulfate. However, the authors found that during a two hour interval after prophylaxis these agents showed the smallest percentage inhibition of growth of the remaining bacteria when compared with the other materials tested. The materials producing the greatest inhibition of growth were the citrus fruit juices.

STOESSER, Minneapolis, Minn. [AM. J. DIS. CHILD.]

HEREDITARY LYMPHEDEMA (NONNE-MILROY-MEIGE): REPORT OF A FAMILY WITH HEREDITARY LYMPHEDEMA ASSOCIATED WITH PTOSIS OF THE EYELID IN SEVERAL GENERATIONS. D. BLOOM, New York State J. Med. **41**:856, 1941.

Bloom has studied a family of 37 members in four generations showing a unique association of lymphedema of the lower extremities and ptosis of one or both eyelids. Six members had the lymphedema and the ptosis and 3 the ptosis only.

The author discusses the occurrence of inflammatory attacks, the association with spina bifida occulta, the presence of mental deficiency and the genetic mechanism of the disorder.

RONCHESE, Providence, R. I.

PALPEBRAL MANIFESTATIONS OF TERTIARY SYPHILIS. G. RENARD and P. HALBRON, Arch. d'opht. **2**:599 (July) 1938.

Renard and Halbron present figures to show that tertiary syphilis of the lids is rare. They report on a patient who had first infectious blepharitis and then syphilitic ulceration. The exact nature of the disease was suspected because of the resistance to various types of treatment and was confirmed by serologic study. Treatment with iodides and mercurials resulted in a rapid cure. The authors point out that tertiary syphilis of the lids has many different characters. The conjunctiva may be attacked. Sometimes it is chemotic and infiltrated and forms a grayish flattened mass simulating a false membrane. The bulbar conjunctiva may be affected. The preauricular and submaxillary glands on the infected side become enlarged, hard and freely movable. Renard and Halbron point out that the disease of the lids may be associated with other stigmas of syphilis and with gumma elsewhere. Sometimes the palpebral gumma resembles chalazion. It is remarkable how completely and rapidly it is affected by treatment. Photographs of their patient reveal the progress of the condition.

A NEW SYNDROME: IRITIS AND ACUTE ULCERS OF THE MOUTH AND OF THE VULVA; ITS RELATION TO CURRENT IRITIS WITH HYPOPYON. L. WEEKERS and H. REGINSTER, Arch. d'opht. **2**:697 (Aug.) 1938.

The authors point out that iritis and acute ulcers of the mouth and of the vulva were first observed in 1937, and they give references to the literature. They report a case under observation. They draw attention to the rare condition of recurrent iritis with hypopyon, which is believed to occur exclusively in men. The clinical picture is reviewed. They report a case of this condition in which there were coexisting ulcers of the mouth and of the skin of the genitals similar to those which occur in women. They wonder whether the two conditions are not related. The etiologic factor of these conditions is obscure. Because of the variety of organisms which have been incriminated, the tubercle bacillus most often, the authors suggest that this condition be called recurrent allergic uveitis with hypopyon.

S. B. MARLOW. [ARCH. OPHTH.]

EOSINOPHILE GRANULOMA (PROLIFERATIVE RETICULO-ENDOTHELIOSIS). A. PASINI, Gior. ital. di dermat. e sif. **81**:1 (Feb.) 1940.

Pasini describes the case of a 69 year old woman showing two deep red, irregularly round, raised, smooth, firm, indolent lesions, one located on the forehead and two below each ear. The sections showed an infiltrative-proliferative process mostly made up of histiocytes and lymphocytes, with a predominance of eosinophils scattered in large quantity everywhere. The lesions disappeared almost completely with roentgen ray therapy. Tuberculosis, syphilis, epithelioma, sarcoma and lymphoblastoma are discussed. Pasini concludes in favor of the eosinophile granuloma of Nanta and Gadrat.

Good illustrations and two colored histologic plates accompany the paper.

THE ETIOLOGY OF PSORIASIS INVESTIGATED ACCORDING TO THE METHOD OF LINDENBERG. M. RONZANI, Gior. ital. di dermat. e sif. **81**:769 (Oct.) 1940.

Lindenberg, in Brazil, inoculated experimental animals intratesticularly with blood serum of psoriatic patients in an effort to demonstrate a virus as the pathogenic agent of the disease. The testes were preferred because they were used by Noguchi for the enrichment of the virus of smallpox. Lindenberg claimed to have reproduced lesions of pemphigus and psoriasis in 64 per cent of his guinea pigs. His work later included neurodermatitis, lupus erythematosus and alopecia areata.

Ronzani inoculated 37 guinea pigs with serum from 10 psoriatic patients. The results were completely negative. Other investigators, including the reviewer, repeated these experiments with negative results.

A Rare Pathologic Observation of Visceral Syphilis: Macrogummas of the Heart. D. Mariotti, Gior. ital. di dermat. e sif. **81**:1043 (Dec.) 1940.

Mariotti reviews the literature on the subject and shows the rarity of this finding in thousands of autopsies. He reports 2 cases of large multiple gummas of the myocardium. In 1 a large part of the myocardial tissue was replaced by syphilitic granulomatous tissue. In the other clinical symptoms were absent until the lesions expanded to the inside wall of the ventricle in the form of endocardial sclerosis, formation of thrombi and pulmonary embolism. The condition is almost impossible to diagnose clinically. The case of the intracardiac thrombosis is an exceptional one.

Ronchese, Providence, R. I.

Initial Lesions of Mal del Pinto (a New Dermatosis). Fernando Latapí and Francisco León y Blanco, Medicina, México **20**:315 (July 10) 1940.

In the late 1920's Herrejón published the results of his study on mal del pinto which disproved the theory of mycotic origin and established the spirochetal nature of the disease. Herrejón's work shed light on the clinical course and manifestations of pinta, but the present report is the first to supply knowledge of the early phase of the disorder.

The authors have shown that an erythematosquamous eruption, popularly known as *empeines*, is the first manifestation of the disease. While the lay populace had always regarded *empeines* as the first stage of pinta, dermatologists had never connected the two conditions. Herrejón erroneously regarded *empeines* as an unclassified dermatomycosis because, in contrast to pinta, it is not constantly associated with a positive Wassermann reaction and the lesions can be made to disappear by antimycotic applications.

The initial chancre which followed the intradermal inoculation of one of the authors with serous fluid obtained from a typical lesion of pinta was followed not by the leukomelanodermic changes of pinta but by erythematosquamous lesions identical with *empeines*. Treponema herrejoni was recovered from the lesions of all subjects with the experimentally produced disease and later from those of patients with *empeines*. The evolution of the experimental disease was uniform: On the seventh day a small lenticular papule began to develop at the point of inoculation; this reached its maximum development in about twenty days. Scales then began to form, and after thirty days the lesion flattened out into a round plaque, about 1 cm. in diameter, which became deeply pigmented in dark-skinned patients.

The initial plaque enlarged by peripheral extension or by coalescence with satellite papules. Growth was so slow that after two or three months the plaque was only 2 to 3 cm. in diameter. It remained solitary for three to nine months, after which dissemination set in. The generalized eruption consisted of lenticular pinkish lesions, usually few but sometimes numerous. After one or two weeks the lesions assumed a hamlike hue if the skin was light or became slate colored if it was dark, and then they began to scale. At this stage the lesions were identical with those of naturally acquired pinta. The serologic reactions for syphilis were negative, while the primary lesion alone was present and became positive after dissemination had occurred (two hundred and forty-one days in 1 case and four hundred and ninety-seven days in the case of the authors).

The authors' clinical descriptions and comment are based on study of a number of patients with the naturally acquired disease.

The primary plaque is located on the lower extremities in 80 per cent of the cases, on the upper extremities in 10 per cent, on the thorax in 5 per cent and on the face in 5 per cent. As in the experimental disease, dissemination does not occur until two to six months, and in some instances two to five years, after the primary plaque develops. The secondary stage is ushered in by the appearance of from one to several dozen lesions morphologically identical with the primary erythematosquamous plaque and called pintids by the authors, in analogy to

syphilids. A few months after the appearance of the first crop of secondary lesions a new crop develops, followed at intervals, the duration of which has not yet been determined, by similar eruptions. Though intercurrent febrile conditions may result in temporary or permanent disappearance of the secondary lesions, spontaneous involution of the eruption does not take place. The pintids may be localized, or they may have a generalized or semigeneralized distribution, which is usually asymmetric. Uncovered areas are preferred; the scalp, axillas and genitalia are not involved. Pintids differ from all other erythematosquamous lesions; they are identified by a triad of characteristics: erythema, scaling and dyschromia. In the beginning the lesions are purely erythematous; scaling begins only after one or two weeks. Some dyschromic change occurs early, as evidenced by hyperpigmentation visible on diascopic pressure, but such changes become visible to the naked eye only much later; finally, depigmentation resembling that seen in maculoanesthetic lepra begins. In the end stage, that phase of the disease previously known and studied, the only sign is the presence of large depigmented areas. The size of the plaques varies considerably; recent lesions may be 2 to 3 mm. in diameter, while large plaques on the lower extremities may reach a diameter of 30 cm. or more. The lesions are round, or more seldom oval, in the beginning; later their outlines become polycyclic, and they greatly resemble recurrent syphilids. Their color varies tremendously; the average lesion is ham colored, but scaly plaques appear whitish and older dyschromic lesions may be lead colored or depigmented. Dyschromic plaques often have a checkered surface caused by alternating patches of erythema and pigmentary change. The characteristic feature of the pintid is its sharp, sometimes raised or lichenoid margin, which is often more active than the center and may appear as a ribbon 2 to 3 mm. in width. Activity of the center decreases in older lesions but never completely subsides, as is shown by the presence of many erythematosquamous half-circles, which stand out against the dyschromic background. This feature is characteristic (arabesque-like pintids). Pruritus, as evidenced by scratch marks, hemorrhagic crusts or pyogenic complications, may be present. Secondary infections may considerably alter the clinical appearance of the pintids and, since spirochetes are present in the seropurulent secretions of oozing lesions, may lead to transmission of the disease.

The lymphatics are often involved; the swelling, which is not pronounced, is of the type observed in syphilis.

The following clinical varieties are observed: psoriasiform (50 per cent) either in location (elbows, knees and extensor surfaces) or in appearance (intense scaling, circinate and gyrate contours), "en capa" (33 per cent)—the sleevelike envelopment of the extremities, especially the lower—dermatophytoid (8 per cent), syphiloid (5 per cent), leproid (4 per cent) and polymorphous.

Though T. herrejoni is found invariably, it is more easily demonstrated in the dyschromic than in the erythematosquamous lesions. In 87 per cent of the authors' cases the results of complement fixation and precipitation reactions for syphilis were positive. The reaction was usually moderately positive, while in all previously reported cases of pinta, which were of the fully developed dyschromic form, the reaction was invariably strongly positive. The difference is explained by the slow development of the serologic changes of the disease.

Eosinophilia, which increases in intensity with the duration of the disease, is a constant symptom, but its significance must be interpreted with caution because of the prevalence of intestinal parasitic infection.

Pintids have no specific histologic characteristics; their microscopic appearance varies with their clinical aspect.

Since the spirochetes of syphilis and pinta are nearly identical and since similar serologic reactions are encountered in the two diseases, diagnosis must be made clinically. The authors consider the differentiation of pintids from the lesions of syphilis, psoriasis, dermatomycosis and lepra in detail.

The prognosis is good, and any spirocheticidal drug is effective.

OBERMAYER, Los Angeles.

# Society Transactions

## SAN FRANCISCO DERMATOLOGICAL SOCIETY

H. V. ALLINGTON, M.D., *Chairman*

ERVIN EPSTEIN, M.D., *Secretary-Treasurer*

*Dec. 5, 1941*

**Scleroderma.** Presented by DR. NORMAN N. EPSTEIN.

G. S., a 50 year old Italian, was first seen in the University of California dermatologic clinic on Nov. 25, 1941. Tightness and hardness of the skin had appeared about six years previously. The hands were involved first. They now present some sclerodactylia, with a bluish, waxy and erythematous cast to the skin. Palm-sized and bandlike areas of involvement have appeared on the trunk, the right thigh and the feet. No febrile episode, muscular soreness or eruption preceded the illness.

No treatment has been given.

A general physical examination revealed no abnormalities. The urine and blood count were normal. The plasma cholesterol value was 88 mg. per hundred cubic centimeters and the basal metabolic rate + 8 per cent. A histologic section from the lesion on the right thigh is presented.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: Dr. Maynard has treated some of his patients with scleroderma with high doses of vitamin D and has claimed good results. It might be well to try dihydrotachysterol in this case.

DR. FRANCES A. TORREY: Cases have been presented before this society in which a pancreatic extract was being tried (ARCH. DERMAT. & SYPH. **45**:612 [March] 1942). It would be interesting to know how those patients have progressed.

DR. H. V. ALLINGTON, Oakland, Calif.: Dr. Ervin Epstein and I have followed 2 patients at the Alameda County Hospital with this type of scleroderma who have been treated with insulin-free pancreatic extract. They both are improving, but very slowly. They have also been given ketogenic diets, large doses of vitamin D, thyroid and other medicines; so it is difficult to be sure what is helping.

DR. G. V. KULCHAR: Most of the drugs used in treatment of this condition are vasodilators like pancreatic extract. Acetylbetamethylcholine (mecholyl) has also been used. There is a new preparation, carbaminoylcholine (doryl), which is much more effective than acetylbetamethylcholine.

DR. N. N. EPSTEIN: This man's lesion has apparently cleared spontaneously to some extent. As I understand it, there was much more induration a year ago than there is now. In the English literature it is stated that scleroderma and dermatomyositis are one and the same disease and that acrosclerosis is simply another form of this condition.

**A Case for Diagnosis (Ulcer of the Back).** Presented by DR. FRANCES A. TORREY.

F. McM., a 44 year old road worker, entered the University of California Hospital dermatologic service on Nov. 26, 1941. An ulcer of the back had appeared three and one-half months previously and had gradually extended. It was situated

in the site of a scar that had resulted from a painless vesicular dermatitis three years previously. The ulcer was 5 by 7 cm. in size, with a reddish, papular, nonundermined border and with widespread surrounding inflammation.

Prior to being seen here, the ulcer had been treated with a variety of topical preparations. The acute inflammation had followed the application of butesin picrate.

Treatment here has included boric acid and potassium permanganate compresses as well as 5 per cent sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) cream.

The patient's general condition is good except that he has a probable peptic ulcer.

The urine was normal. Examination of the blood on three occasions revealed a hemoglobin content of 106 to 125 per cent, red blood cells ranging from 6,000,000 to 7,000,000 and leukocytes ranging from 9,100 to 15,600, with 48 to 63 per cent polymorphonuclear cells, 27 to 36 per cent lymphocytes, 4 to 11 per cent monocytes and 5 to 6 per cent eosinophils.

DISCUSSION

DR. G. V. KULCHAR: Were any bacterial cultures made? The condition looks like gangrenous pyoderma to me.

DR. F. G. NOVY JR., Oakland, Calif.: I thought the condition might fall in that group of anaerobic infections that Dr. Kulchar referred to. When was the butesin picrate applied? I know that a reaction from that will last a long time.

DR. FRANCES A. TORREY: I have not done any extensive culture work. I felt that cultures would not give a true picture of the underlying infection in view of the complication of dermatitis venenata. The butesin picrate was used about three days before he came to me with the acute lesion. The ulcer, as far as I can determine from his history, began suddenly as a small lesion and has grown gradually. He had a scar in this area from a lesion which he called "herpes." I felt that this case was similar to that of the elderly physician who was seen here a year and a half ago with a lesion on the abdomen which spread in much the same manner. There was, however, severe systemic involvement in that case.

DR. ORLAND F. MONTGOMERY: I suggest zinc peroxide therapy. I have seen 2 patients who did well with thorough cleansing of the lesion and the use of zinc peroxide.

DR. FRANCES A. TORREY: I used zinc peroxide on the other patient I mentioned, but it was not very successful. The patient began to improve after potassium permanganate compresses were used.

DR. F. G. NOVY JR.: I think that when the dermatitis venenata subsides you may find that many of the ulcers will heal.

**A Case for Diagnosis (Epithelioma? Syphilis?).** Presented by DR. JOHN M. GRAVES.

H. W., a 56 year old white man, a highway worker, came to the University of California dermatologic clinic on Jan. 17, 1941, complaining of a crusted lesion in a scar on his back. About ten years previously he had had a red nodule in the interscapular area. This had been incised several days after its inception but failed to heal. It gradually extended, over five years, until it encompassed an area almost as large as the present scar. Five years before he came to the clinic he received several roentgen ray treatments at Stockton, Calif., but the lesion persisted. The lesion was removed by electrodesiccation three and one-half years before I saw him, and the pathologic report was squamous cell epithelioma. Two small neoplasms were removed from other areas on the back by electrodesiccation in 1939. A cancer of the testicle was removed in January 1939.

On physical examination in January 1941 no other abnormalities were found. A roentgenogram of the thoracic portion of the spine showed no evidence of

metastases or of inflammation. Kolmer and Kahn tests elicited negative reactions. The patient had a telangiectatic scar with circinate borders, about 13 by 17 cm. in size, between the scapulas. A crusted lesion 1.5 by 1.5 cm. was situated in the center of the scar. The administration of potassium iodide three times a day was started on January 29, and two injections of iodobismitol were given as a therapeutic trial, without effect. A biopsy revealed inflammatory reaction only.

On about November 11 a new lesion appeared several centimeters to the left of the previous one. This is an ulceration 1.5 by 1.5 cm. deep, and with a smooth papular reddish border. A biopsy of excised tumor showed epidermoid carcinoma.

DISCUSSION

DR. C. J. LUNSFORD, Oakland, Calif.: There is a history of squamous cell epithelioma in this case. It seems to me that the first consideration here is a malignant growth.

DR. N. N. EPSTEIN: One should not forget that this man had a teratoma of the testicle removed two or three years ago. Examination shows two small nodes in the groins. The lesion on the back may be metastatic from this tumor.

DR. JOHN M. GRAVES: As I see the sections today, I do not think there is much question that the man has an epithelioma. However, originally the question of syphilis was raised, and I do not believe it is settled yet. He had a little treatment and then returned to Stockton. He was supposed to continue antisyphilitic injections but did not do so. He has not had an adequate therapeutic test to determine whether or not there is a syphilitic background.

DR. N. N. EPSTEIN: Do you not think that the histologic section is unusual in regard to cell type?

DR. JOHN M. GRAVES: There is one place that shows characteristic epithelial cells which I think any one would call epithelioma.

DR. G. V. KULCHAR: There has been a recent report in which it is stated that epitheliomas arise on tertiary lesions. This new lesion certainly is clinically squamous cell epithelioma.

DR. H. E. MILLER: When I first saw this patient I thought that he might have syphilis. A separate lesion developed, and the pathologist made a microscopic diagnosis of metastatic malignant growth. I think that if this is true one can forget the syphilitic infection. It does not make any difference to me whether he had the therapeutic test for two weeks or for six months. The primary growth undoubtedly was not in the skin.

DR. H. V. ALLINGTON, Oakland, Calif.: Could you tell whether the growth is metastatic from the teratoma or from the malignant lesion of the skin?

DR. FRANCES A. TORREY: The pathologists would not commit themselves as to that.

**Synovial Cysts.** Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

Mrs. R. S., a 40 year old white woman, was first seen in June 1941, complaining of a swelling on the distal joint of her right index finger of one year's duration. Several months previously an attempt had been made to remove the lesion surgically, but it had recurred almost immediately. A similar lesion then developed on the side of the distal joint of her right middle finger.

The patient presented lesions the size of a split pea in the aforementioned locations. The swellings were definitely cystic. On her index finger the lesion was oblong and the long axis ran transversely across the finger.

Both lesions were treated with roentgen rays, 200 r being administered at 125 kilovolts through a filter of 1 mm. of aluminum. This resulted in definite improvement. The lesion on the middle finger has nearly disappeared. The one on the index finger improved, but recently it has started to grow again and has become tender.

**Synovial Cyst.** Presented by Dr. Ervin Epstein, Oakland, Calif.

L. G. S., a 41 year old man, the husband of R. S., noted an asymptomatic, slowly growing nodule on the distal joint of his left index finger at about the same time that his wife first noted her lesions. This nodule has not been treated. It is on the extensor surface of the finger. There is some hyperkeratosis of the overlying skin. This lesion is translucent and roughly the size of a split pea.

DISCUSSION OF TWO CASES OF SYNOVIAL CYST

Dr. H. E. Miller: I believe that the man has a synovial cyst on his finger, but I could not be certain that the woman had synovial cysts. I have seldom seen a patient with more than one cyst of this kind. Neither of these patients had signs of arthritis or rheumatism on their fingers. It is unusual to find this condition in patients of their age.

Dr. C. J. Lunsford, Oakland, Calif.: I had a patient in her sixties. She had synovial cysts on the dorsa of four fingers. She also had arthritis. She was treated unsuccessfully with radium.

Dr. Orland F. Montgomery: I should like to hear more about therapy in cases of this kind. In some books it is stated that roentgen rays cure such conditions.

Dr. H. J. Templeton, Oakland, Calif.: It has been my experience that treatment of these lesions is extremely disappointing. I have tried roentgen rays and radium. I have tried electrocoagulation, as one would with epitheliomas. I have cauterized the sacs. With every method I have had recurrences. These lesions are connected with the deeper synovial system. I think that therapy directed toward the lesion on the surface is more apt to fail than to succeed.

Dr. Orland F. Montgomery: Is the lesion a hernia?

Dr. H. E. Miller: My therapeutic procedure at present is to explain to the patient that the lesion can be removed for cosmetic purposes but that treatment is not always successful. I treat the lesion with roentgen rays, 1,000 to 1,500 r. I explain that if this will cure the lesion it will take two to six months to do so. Under such treatment, fibrosis and closing of the sac occurs.

Dr. A. E. Ingels: I do not see why one should go to all that trouble when it is easy to peel the lesion out.

Dr. H. V. Allington, Oakland, Calif.: Do you cure it by that means?

Dr. A. E. Ingels: You do if you get the whole sac.

Dr. Ervin Epstein, Oakland, Calif.: In regard to the diagnosis in the case of the woman, a physician attempted to remove one of the lesions. He stated that it contained the typical glossy mucus. I gave her only 200 r of roentgen rays and one of the lesions almost disappeared and the other improved considerably. I had another patient whose lesion cleared up after an extensive removal by cautery, but with a poor cosmetic result. My last 4 patients were all older than 40. This condition is sometimes confused with warts and with molluscum contagiosum. In all probability the simultaneous appearance of these comparatively unusual tumors in a husband and wife is just a coincidence. However, one cannot help speculating on the possibility of a virus infection's being the cause of the nodules, as in verruca and in molluscum contagiosum.

**A Case for Diagnosis (Lymphoblastoma).** Presented by Dr. John M. Graves.

H. S., a 59 year old white man, is presented from the University of California dermatologic clinic. He has about eight cutaneous lesions, which have appeared at different times during the past five years and which have been slowly progressive. They are distributed over the forehead, the nape of the neck, the back, the arms and the thighs. They are plaquelike and definitely infiltrated, with smooth, rolled borders. The color varies from light brown to brownish violet. The erup-

tion is asymptomatic. His general health is good. For seven months the patient has had bilateral chronic simple glaucoma.

The results of urinalysis and the blood count were within normal limits. Wassermann and Kahn reactions of the blood were negative.

The oral administration of 1 grain (0.065 Gm.) of phenolphthalein failed to influence the lesions. Roentgen ray therapy in a dose of 75 r to the lesions in the center of the back was given on Nov. 11, 1941.

Histologic sections show a polymorphous cell type of perivascular infiltration in the midcutis. The specimens for biopsy were taken from the lesion on the right thigh. Histologic sections are presented.

DISCUSSION

DR. G. V. KULCHAR: The biopsy did not reveal a definite picture, but clinically the disease looks like generalized granuloma annulare.

DR. A. E. INGELS: Because of the uniformity of the cell type in the cutis, I felt that the lesion would not conform to a lymphoblastoma. The presence of some groups of foam cells suggest sarcoid. From this one section, I was unable to make a definite diagnosis. I know that foam cells are characteristic of sarcoid, leprosy, rhinoscleroma, etc. I feel that it would be necessary to study more sections before I could subscribe to a diagnosis of sarcoid. I am against a diagnosis of lymphoblastoma from the histologic sections.

DR. J. M. GRAVES: The diagnosis is questionable. When I first saw this patient, I felt that he probably had a sarcoid. I felt disappointed when the sections did not bear that out. However, they did not bear out any other diagnosis, as far as I could tell. The man was questioned rather closely about the use of drugs. I do not know what is meant by a "generalized granuloma annulare."

**Psoriasis.** Presented by DR. FRANCES M. KEDDIE (by invitation).

This patient was previously presented before this society on Sept. 20, 1940 (ARCH. DERMAT. & SYPH. **43**:871 [May] 1941).

After the previous presentation, the patient was given three pyretotherapy treatments, with a temperature of 40 to 40.8 C. (104 to 105.4 F.) maintained for five hours. These effected a considerable change in the appearance of the eruption. The keratotic excrescences fell off, leaving erythematous and purplish scaling areas.

The patient returned to the clinic in November 1941 with lesions characteristic of psoriasis.

DISCUSSION

DR. N. N. EPSTEIN: I think that every one will remember this woman. The question of whether the condition was keratosis blenorrhagica or pustular psoriasis was debated. I am not certain that her present lesions prove that her condition was psoriasis at that time. I think that she could have had a keratosis blennorrhagica.

DR. C. J. LUNSFORD, Oakland, Calif.: I think that therapy in cases of intragluteal and peroneal psoriasis is difficult. I should like to hear some discussion of therapy for psoriasis in these particular locations.

DR. H. E. MILLER: Roentgen ray therapy is not satisfactory. I treat patients with this condition with 0.1 per cent anthralin (dihydroxyanthranol). It works well in most instances.

DR. F. M. KEDDIE (by invitation): The patient states that the lesions she has now are exactly the same as the lesions she had some years ago.

**Mycosis Fungoides.** Presented by DR. H. E. MILLER.

A. J., a white man aged 35, was first seen at the University of California dermatologic clinic in November 1941. He complained of pruritic cutaneous

lesions and loss of weight and strength of three years' duration. The condition began with a patch of erythroderma on the right thigh, and new lesions progressively appeared over the entire body. A year ago papular infiltrated lesions appeared on his face, and later they developed elsewhere. Two months ago a tumor appeared on the right temple. Additional tumors have appeared since then on the face and on the abdomen.

A general examination revealed no abnormalities except for some loss of weight, the cutaneous lesions and enlarged, discrete, nontender, semifirm lymph nodes on his neck and in the axillas and groins.

The urine was normal. A blood count was normal except for showing 5 per cent eosinophils. The calcium content of the blood serum was 7.6 mg. per hundred cubic centimeters and the phosphorus content 2.6 mg.

Treatment before the patient was seen here had included fractional doses of roentgen rays to the individual lesions and malarial fever therapy.

He entered the University of California Hospital on Nov. 10, 1941. Treatment has included radioactive sodium phosphate orally, 0.92 millicuries on November 12 and 1.52 millicuries on November 29. Histologic sections are presented.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: I should like to ask Dr. Miller if any of the radioactive cyclotron products have been tried in cases of mycosis fungoides.

DR. FRANCES A. TORREY: I talked to Dr. Friedell, who has been giving the patient radioactive sodium phosphate. They found three times as much of the radioactive substance in the lymph nodes as in the skin. There was a measurable quantity in the skin, but not very much. The cutaneous lesions and the normal skin contained the same amount of the radioactive salt.

DR. A. E. INGELS: Darkfield examination according to the Hoffmann technic might be of value in determining more exactly where the radioactive salt has been deposited.

DR. H. E. MILLER: I have always felt that it was a mistake to use radioactive phosphorus in the treatment of mycosis fungoides. It is deposited in the bones and not in the skin. Arsenic is deposited in the skin and would be the drug of choice. I also objected to the use of arsenic because it would be impossible to determine whether it was the arsenic or the radioactivity that caused the improvement. This man has reached a point where his lesions are no longer amenable to roentgen rays. It is a poor time to determine the therapeutic value of any radioactive substance.

**Lymphoblastoma.** Presented by DR. R. A. STEWART.

H. A., a 61 year old Jew, was first seen on July 6, 1940. At that time he had indurated, purplish, coin-sized lesions symmetrically distributed over the head and face. These lesions were confluent on the forehead and eyebrows and resembled a vascular nevus. They had been present for about six months. There were dime-sized, plum-colored, nodose lesions symmetrically arranged on his shoulders and on the upper part of the trunk. There was a generalized lymphadenopathy, most pronounced on the neck and in the inguinal regions. The results of the remainder of the physical examination were essentially normal. The blood count was as follows: red cells 5,090,000 and white cells 6,600, with neutrophils 63 per cent, lymphocytes 34 per cent, mononuclear leukocytes 1 per cent and eosinophils 2 per cent. The hemoglobin content was 82 per cent. Biopsy of a specimen taken from the scalp showed chronic inflammatory changes.

The patient was given arsenic in the form of asiatic pills, 1/9 grain (7 mg.), and fractional roentgen ray therapy at weekly intervals. By the end of September 1940 the cutaneous lesions and the lymphadenopathy had disappeared almost entirely.

The patient did not report again until April 1941, after an absence of seven months. At that time he was acutely ill. He stated he had been treated by a roentgenologist, who had given him roentgen therapy of high voltage, in doses similar to those used for cancer. Physical examination revealed exophthalmos, moderately sized lymph nodes in the left side of the neck and a large amount of fluid in the left pleural cavity. The liver was enlarged, and numerous hard palpable masses were felt throughout the abdomen as well as much free fluid. The fluid, obtained by paracentesis, was chylous and suggested invasion or obstruction of the lymphatic system by the pathologic process.

The patient was given superficial fractional roentgen ray therapy to the new lesions and was symptomatically improved to some extent. In November 1941 pruritus became distressing.

DISCUSSION

DR. H. E. MILLER: I think it would be difficult to make a positive diagnosis at this time. During the course of the disease the patient has had numerous plaques that seemed to be characteristic of a lymphoblastoma. From a therapeutic standpoint, there was involution under 75 r of filtered roentgen rays. At one time, at one of the local hospitals, he was given cancer doses of roentgen rays. He became very ill after this, and ascites developed. When he was given a dose of 75 r, he improved generally and was able to resume his employment.

DR. R. A. STEWART: My reason for presenting this patient was to show that one does not need to give large doses of roentgen rays to control the cutaneous lesions. I think that he may need another series of superficial radiation treatments in a few months.

DR. ORLAND F. MONTGOMERY: How many areas do you treat at one time?

DR. R. A. STEWART: I have seldom treated more than six at one time.

**Foreign Body Granuloma or Interdigital Cysts with Hair Formation.**
Presented by DR. H. J. TEMPLETON, Oakland, Calif.

D. H., a man aged 27, was presented previously before this society on Sept. 19, 1941 (ARCH. DERMAT. & SYPH. **45**:614 [March] 1942).

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: This patient alleges that he acquired his lesions as a result of his occupation. He is a barber. He states that the hairs enter the interdigital webs and that he can express from the sinuses hairs of different colors, which are hairs of his customers. On several occasions I have seen those areas become acutely inflamed. On one occasion, while I was probing around, I got hold of a pearly white glistening sac and extracted it in toto. In this sac there were many hairs. It was sent to the pathologist. He reported that the sac must have originated in the patient and that the hairs were from the lining of the sac. The hairs were short, and the ends were cut off, as if they had been cut by scissors. The pathologist stated, however, that that might have been done by the microtome. I should like to know whether one should consider this an occupational disease.

DR. G. V. KULCHAR: Trichostasis spinulosa occurs in other locations with the same sort of reaction.

DR. F. G. NOVY JR., Oakland, Calif.: I think that if these cysts arise from the skin the hair should probably be curly and rather immature and that if the hair is from customers' heads it should be short and stubby. It is rather hard to think of the adult type of hair forming in a cyst.

DR. H. J. TEMPLETON: Does a foreign body ever produce a glistening sac?

DR. A. E. INGELS: What puzzles me is how the patient could produce such lesions himself.

DR. H. V. ALLINGTON, Oakland, Calif.: I have wondered if the patient's condition could be a congenital anomaly in the formation of the interdigital webs, with cyst formation and sinuses into which hairs are accidentally forced.

DR. N. N. EPSTEIN: I believe that this condition is a foreign body type of reaction. I think the hairs come from outside. Some barbers have told me that when they come home at night they sometimes find hairs sticking in the skin of various parts of the body.

DR. ORLAND F. MONTGOMERY: Why does it occur on one hand only? Would not a man remove the hairs he sees on his hands?

DR. EDWARD A. LEVIN: Have the patient wear rubber gloves when he does his work. That will cure him.

**Pemphigus Vegetans.** Presented by DR. FRANK K. HAIGHT (by invitation), Oakland, Calif.

H. H. P., a 55 year old man, an American railway signal man, consulted me on Oct. 2, 1941, having been referred by Dr. George Irvine, of Oakland, Calif. At that time his complaint was an eruption in both axillary areas, on the flexor surfaces of the elbows, on the entire lower part of the abdomen and on the thighs and legs. The duration of the eruption is approximately four years.

The patient stated that in May 1937, while trimming some trees on a railroad right of way, he came in contact with poison oak. A severe dermatitis developed, which, he states, became secondarily infected. After a few weeks it cleared up uneventfully. Two months later he suffered a series of carbuncles involving the hips and buttocks. He was treated by a local physician for this and made an uneventful recovery.

About three months after the subsiding of the carbuncles, the patient noticed the sudden appearance of a group of small blisters, varying in size from that of a small grain of rice to that of a pea. These appeared in both groins and varied in number from four to twenty. He ruptured these and applied a preparation of sulfur and lard. This led to the development of denuded areas, which gradually subsided and relieved him of the pain and burning sensation which always accompanied the outbreak of these lesions. In a few days a second crop would follow the first, each one arising rapidly, almost overnight, always on areas of clear skin. As time went on, the size of these blisters gradually increased until they became roughly the size of a quarter and extended upward onto the abdomen. Two and one-half years ago they became more bullous, increased considerably in size and would rupture more or less spontaneously from the friction produced by his clothing. These ruptured bullae left large denuded areas, which were accompanied by considerable burning and itching. By coalescence of the smaller areas, relatively large geographic ones were formed. At no time have any lesions ever appeared on the mucous membranes.

During the past two years the eruption has been more or less constantly present, with gradual extensions, particularly into the axillas and on the flexor surfaces of both arms and involving the thighs and legs. These lesions at times appear in groups, almost resembling warty vegetations. They always arise from normal skin.

The picture presented tonight is somewhat altered from what I have just described, because of therapeutic measures; there are few if any of the wartlike vegetations present.

The Wassermann reaction was negative, the sedimentation rate of the blood normal and the urine normal. He has a mild secondary anemia and a normal white blood cell and differential count with the exception of 8 per cent eosinophils. His temperature has always been normal. A physical examination revealed nothing abnormal.

Treatment has consisted largely of massive doses of vitamin D by mouth, varying from 90,000 to 160,000 U. S. P. units a day. He has been given some filtered roentgen ray therapy, 100 r at weekly intervals, and in all has had five such treatments. He is using a sulfathiazole (2-[paraaminobenzenesulfonamido]-

thiazole) ointment locally. He is also receiving sodium cacodylate and liver extract intramuscularly. His condition has considerably improved.

DISCUSSION

DR. ERVIN EPSTEIN, Oakland, Calif.: I saw this patient with Dr. Haight two months ago. At that time the clinical appearance was that of pemphigus. I think the imrovement the patient has shown in two months is remarkable.

DR. H. E. MILLER: I saw this man a year or more ago. I made a diagnosis of pemphigus at first and then changed it to dermatitis herpetiformis; I still believe that the condition is dermatitis herpetiformis. The pigmentation, the vesicles and the polymorphous character of the eruption make me believe that this is the diagnosis. The remissions are also of importance. While under my care the patient never had any lesions in his mouth. His general health has been excellent during the course of the disease. I gave him sulfanilamide and the condition cleared spectacularly. In less than a week after he discontinued this treatment, the lesions recurred.

DR. H. J. TEMPLETON, Oakland, Calif.: I agree with Dr. Miller. I think this condition is dermatitis herpetiformis. I should like to suggest trying dihydrotachysterol, at first 3 cc. and increasing to 5 cc., with the serum calcium content being checked frequently. I had a patient with extremely severe pemphigus vulgaris. He was a mass of foul, stinking blebs, with involvement of the mucous membranes, and was apparently ready to die. I gave him dihydrotachysterol, and in one week he was free of his eruption. Then I went on my vacation. When I returned the blebs began to reappear. I gave the patient dihydrotachysterol again, but the disease progressed and he died.

DR. H. E. MILLER: I have tried dihydrotachysterol a few times without any success.

DR. A. E. INGELS: I think a biopsy should be made to establish the diagnosis. There are sufficient histologic characteristics to differentiate pemphigus and dermatitis herpetiformis. The latter shows multilocular vesicles under the horny layer intraepithelially and subepithelially as the most characteristic feature. Pemphigus, on the other hand, shows unilocular vesicles, or bullae. Besides, there are many other characteristics to establish a correct diagnosis.

DR. STUART C. WAY: A diagnosis in early pemphigus is not always possible. When Dr. Epstein's case was first observed by Dr. Graves and later by me the condition was clinically typical of dermatitis herpetiformis.

DR. N. N. EPSTEIN: The patient mentioned by Dr. Way was given dihydrotachysterol and became very ill. The disagreeable odor was decreased by this therapy, but the lesions were uninfluenced.

DR. H. E. MILLER: I wish I could agree with Dr. Ingels that one can differentiate dermatitis herpetiformis and pemphigus by biopsy. I do not take a specimen for biopsy routinely as I do not believe that one can differentiate the two diseases under the microscope.

DR. F. K. HAIGHT (by invitation), Oakland, Calif.: This is one of the reasons I do not perform a biopsy. I lean toward the diagnosis of pemphigus in this case. When I first saw this patient the eruption was vegetative, actually resembling grapes. I made a patch test with iodine, but it elicited no reaction.

The patient responded well to sulfanilamide and also to sulfathiazole. Now he has an intolerance toward these drugs.

**Xanthoma Tuberosum Multiplex.** Presented by DR. H. V. ALLINGTON, Oakland, Calif.

E. R. M., a white man aged 36, has noted the appearance of lemon yellow, papular lesions on his hands and elbows during the past few months.

These are smooth, dome-shaped lesions, averaging 2 or 3 mm. in diameter. They occur on the volar surfaces of the thumbs and elsewhere on the fingers.

On the elbows, they are grouped on the extensor surfaces and show superimposed hyperkeratosis. The palms have a faint, diffuse, lemon yellow tint. The lesions are tender on pressure but not spontaneously painful.

The patient had pneumonia about a year ago. His average weight has increased about 15 pounds (7 Kg.) in the past six months.

The fasting blood sugar content was 100 mg. per hundred cubic centimeters.

The fasting blood cholesterol content was 909 mg. per hundred cubic centimeters.

DISCUSSION

DR. R. B. REES (by invitation): Do you think there is any tendon involvement? The patient has some tenderness along the fingers.

DR. N. N. EPSTEIN: I think the fact that the patient has such a high blood cholesterol value is a good sign as far as the ultimate disappearance of the lesions is concerned. May I ask why Dr. Allington called this condition the multiplex type of xanthoma tuberosum?

DR. H. V. ALLINGTON: This case is one of xanthomatosis of the hypercholesteremic type. This is true both of xanthoma tuberosum multiplex and of eruptive xanthomas. I believe the latter term is reserved for the more acute and more inflammatory type of lesion often associated with some itching. These may come and go during the course of severe diabetes or in the presence of hyperlipemia without diabetes. This patient's lesions have appeared gradually and persisted. They show no signs of acute inflammation and are symptomless except for slight tenderness on pressure. I do not think he has any tendon involvement.

DR. N. N. EPSTEIN: The acute onset of the condition suggested xanthoma eruptivum to me.

**Parapsoriasis en Plaques.** Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

C. K., a 52 year old white man, consulted me about six weeks ago because of an asymptomatic eruption of one year's duration. The lesions first appeared in the groins and spread to his legs, back, abdomen and arms.

The patient presents multiple yellowish red irregular oval macules in the aforementioned locations. The involvement is most pronounced on his left arm. Scraping the lesions elicits a branny desquamation. Some of the scrapings were examined microscopically after gentle warming in a 20 per cent solution of potassium hydroxide but failed to reveal fungi.

As therapeutic tests, roentgen rays (125 r) were given to one lesion on the right arm; a sulfur ointment was applied twice a day for one week to a lesion on the left arm, and a 20 per cent iodocholeate ointment was applied for a like period to another lesion on the left arm. Other than producing an iodine burn, these agents were ineffective in changing the appearance of the dermatosis.

DISCUSSION

DR. C. J. LUNSFORD, Oakland, Calif.: I have no better diagnosis to offer, but I think it unusual that with such a disease a patient should have itching.

DR. N. N. EPSTEIN: I think that a biopsy is essential to establish that diagnosis.

DR. ERVIN EPSTEIN, Oakland, Calif.: I do not believe the patient's lesions itch, although he has a pruritus ani. I have observed a number of such cases but have not seen the condition in any of them develop into a lymphoblastoma. However, I am watching the patient carefully.

DR. ORLAND F. MONTGOMERY: I thought it was interesting that the first lesion developed in the crural region and no fungi were found.

**Hydrocystoma.** Presented by DR. R. B. REES (by invitation).

Mrs. N. C., aged 63, is presented from the University of California dermatologic clinic. She has had lesions on the face for thirty years consisting of many dis-

crete, sharply defined, clear cysts. These tend to be larger in warm weather. Beads of perspiration can be seen on their surfaces when the patient's face is flushed.

A biopsy section is presented.

DISCUSSION

DR. A. E. INGELS: I thought that the histologic picture was characteristic of hydrocystoma.

**Lewandowsky's Rosacea-Like Tuberculid?** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

Miss M. K., aged 29, was seen on Sept. 26, 1941 because of an atypical rosacea-like eruption of the forehead, cheeks and chin. Reactions to 1:100,000 and 1:10,000 dilutions of tuberculin were negative. The reaction to a 1:1,000 dilution was strongly positive. Treatment has consisted of the administration of diluted hydrochloric acid by mouth and the local application of a strong sulfur ointment.

DISCUSSION

DR. G. V. KULCHAR: I thought in looking over the lesions that there was atrophy, which would not occur in the healing of a tuberculid. The condition looked to me more like that described as folliculitis ulerythematosa reticulata.

DR. H. E. MILLER: It is difficult to make a positive diagnosis in this case without microscopic examination of tissue. However, I believe that the diagnosis as given is correct.

DR. A. E. INGELS: Clinically, I feel that this condition is amyloidosis or a similar degenerative disease. The lesions are semitranslucent, brownish and cyst-like or granular to touch, which would suggest to me a degenerative process. Naturally, the diagnosis would hinge on a biopsy with differential stains.

DR. H. V. ALLINGTON, Oakland, Calif.: I believe the disease is a rosacea-like tuberculid. I think the atrophy in this case, if any is present, is rather indistinct and poorly defined. The lesions individually correspond to those of a rosacea-like tuberculid.

DR. H. J. TEMPLETON, Oakland, Calif.: Here on the Pacific Coast physicians have few opportunities to see Lewandowsky's rosacea-like tuberculid. Therefore I am not very familiar with it. However, in my opinion, my patient has this disease. The rosacea-like eruption spares rather than involves the middle third of her face. There is an absence of any pustular element. As some of the papules disappear their sites seem to be somewhat atrophic.

DR. A. E. INGELS: Do you not feel that it is important that the patient has been in the best of health? She never had tuberculosis, and there was never any in the family. She feels and looks perfectly well and robust.

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## NEW YORK DERMATOLOGICAL SOCIETY

J. GARDNER HOPKINS, M.D., *President*

A. BENSON CANNON, M.D., *Secretary*

*Jan. 27, 1942*

**Nocardiosis.** Presented by DR. HOWARD FOX.

R. N., a boy aged 16 months, was referred for consultation by Dr. Else Barthel. He was first seen by me on Oct. 15, 1941 and showed a pustulosquamous rash on the scalp, about the ears and on the abdomen. There was no erythema surround-

ing the lesions. On the hard palate and surrounding the anus there was a fungating gray growth with an ulcerating surface. There were small lesions at the gingival borders which were covered with necrotic membrane and bled easily on slight trauma. They caused no appreciable pain or tenderness.

The baby looked sick because he had had a rise of temperature and leukopenia following the administration of sulfanilamide. This had been used in the treatment of Vincent's organisms in the mouth. After the reaction subsided the baby looked and acted well. No further Vincent's organisms but numerous gram-positive cocci and rods were found.

A culture was made by Dr. Barthel of the diseased tissue removed from the anal region. It showed a weak growth of a Nocardia with streptothrix-like mycelium. The same growth was obtained from deep scrapings of the oral lesions. The growth was equally sparse on various anaerobic as well as aerobic mediums.

The blood counts were essentially normal except when sulfanilamide was administered. Histologic examination of both anal and oral lesions showed simple inflammation with no suggestion of either tuberculosis or syphilis. Several urinalyses gave normal results. The cutaneous reaction to an injection of old tuberculin in a dilution of 1:1,000 was negative. The Wassermann reaction of the blood of the patient and of both parents was negative.

Treatment has been unsatisfactory, and the baby is now refusing food and has lost weight. Aqueous solutions of gentian violet in concentrations of 1 to 5 per cent were used locally for both oral and anal lesions. The anal lesions were treated with unfiltered roentgen rays (300 r) on three occasions, and radium was used once in the mouth. Gentian violet and iodides were also administered internally. Local treatment with gentian violet was discontinued after having been used for five weeks, and since then local treatment has consisted of saline baths and hydrogen peroxide and, occasionally, sodium perborate and thymol iodide.

DISCUSSION

DR. GEORGE C. ANDREWS: This is an unusual case. The child appears seriously sick, and I think it should be hospitalized again. I should like to know if blood cultures have been made.

DR. EUGENE F. TRAUB: I believe Dr. Barthel's diagnosis has to be accepted in this case. She has not only repeatedly obtained the organism from smears but also cultured it and was apparently able to demonstrate the organisms at will in these lesions at one time. Also the organisms she demonstrates are a type of Nocardia. I believe the prognosis in this case is not good. The child has been rather actively treated and has had intensive irradiation, along with a vast amount of chemotherapy. One suggestion that might be of some benefit is to try an ozonized oil which contains a high percentage of oxygen and which can be used on the mucous membranes of the mouth or rectally without irritation. To date nothing has caused much improvement of the old lesions, while on the other hand extension of the granulations and ulcerations has taken place.

DR. J. GARDNER HOPKINS: This is an extraordinarily interesting case. I should like to ask Dr. Barthel, in closing, what is the differentiation between nocardiosis and actinomycosis? As I understand it, the term nocardiosis has been applied to lesions from which aerobic actinomyces are isolated; some of these lesions resemble actinomycosis. I am unfamiliar with the clinical lesions described in this infection. The other point I want to raise is that in conditions in which fungi are found, the question is to what extent is this fungus responsible? To what extent is the fungus growth due to some underlying metabolic disturbance or underlying infection? I wonder about the possibility of a mixed infection, such as Meleney has described with undermining lesions due to the microaerophilic streptococcus.

DR. ELSE BARTHEL (by invitation): In the literature I could not find any reference to lesions similar to these. In the classification of Nocardia according to the most modern procedures, it does include all the Actinomycetes and Streptotriches. The organism in this case is a Streptothrix rather than the ordinary variety of Actinomyces. This particular organism is difficult to grow. It will

grow for five days and no more. I also looked for anaerobic streptococci. In the beginning, after the Vincent organisms were removed, there were many secondary organisms, but they disappeared after gentian violet was used. There are still thrombi in the vessels. The case has been quite baffling. I thought at first the disease belonged in the tuberculosis group but could find no evidence of it. As far as the child's physical condition goes, he was examined by the pediatrician a week ago, and the hemoglobin was in the average range for his age and there was apparently nothing wrong. When the dose of iodides was increased to 60 grains (4 Gm.) a day he would not eat, but when this medication was discontinued he was willing to eat everything. Lately he has refused all food but milk and eggs and he has been sick with a cold, but he has always had a bad color, even when I first saw him. I believe the outcome will be bad. I made one blood culture early in September, which gave negative results. Since then none has been made. I took blood for culture before the last roentgen ray treatment was given and did not get any growth. This bothered me, since I had obtained it six times before, and yet the lesions still look the same.

**Malignant Melanoma.** Presented by DR. EUGENE F. TRAUB.

T. P. Z., a boy aged 16 months, was first seen as a private patient in March 1941. A large pigmented birthmark, involving the greater part of the left cheek, has been present since birth. The mark was not particularly hairy, although there were some fine and a few coarse hairs present. The center of the lesion seemed to be darker than the rest, and there was a question at this point whether or not a change in character of the nevus was taking place. The patient was referred to a plastic surgeon, who at my suggestion removed the entire growth, on Sept. 17, 1941. A skin graft had been removed from the leg to cover the defect. The patient exhibited a tendency toward keloid formation both at the site from which the graft had been taken on the thigh as well as on the cheek area. Otherwise the healing was uneventful.

Within the last few weeks a number of pigmented spots have appeared in the scar tissue on the cheek. These are superficial; one is almost stellate in shape, and, in my opinion, none has the appearance of a cutaneous metastasis of a malignant melanoma. Since their initial appearance these pigmented spots have increased in size only slightly, if at all. No other symptoms have been noted.

The tissue removed from the cheek originally was reported by the pathologist at Lenox Hill Hospital as a malignant melanoma, and this diagnosis has been concurred in by a number of dermatologic pathologists who have looked at the section.

DISCUSSION

DR. J. FRANK FRASER: Apparently the original lesion was a maligant melanoma. It is a well known fact that when metastases occur from malignant melanomas, the first, chief and favorite site for these metastases is the skin itself. This patient's lesions are possibly metastatic growths, but the probability is that they are benign. I suggest further examinations, such as taking roentgenograms of the chest, before any treatment is undertaken. The keloid is disfiguring, and if there is any known method by which it can be removed, I think it should be tried.

DR. FRED WISE: I should like an expression of opinion with respect to the choice of therapy for such a lesion. I appreciate the gravity of the prognosis based on the histologic observations, but in view of the circumstance that the nevus was a hairy mole, I wonder if treatment with solid carbon dioxide would have been contraindicated.

DR. R. H. RULISON: The skin graft was taken from the child's leg. There is no freckling or other pigmentation of the legs. Yet there is a definite, rather large freckle in the grafted area. I believe this constitutes a recurrence of an incompletely removed melanoma which has invaded the graft from below. I suggest a second wide and deep removal of the entire area, to be followed with a new graft.

DR. EDWARD R. MALONEY: I agree with Dr. Wise. I do not believe the child has a metastatic growth but a recurrence in situ. Possibly if the treatment Dr. Wise suggested were used, it would be beneficial. I think I should leave the keloid alone for the time being.

DR. FRANK C. COMBES: I agree with Dr. Fraser. I should not do anything now about the pigmented lesions except to observe them. I ask why a benign growth that was completely excised should recur in the graft. I should like to ask how often hairy moles become malignant.

DR. A. BENSON CANNON: I think that the only thing one can do is to accept the histologic diagnosis of melanocarcinoma. The pinhead-sized areas that have appeared in the keloidal scar would indicate that all of the melanotic cells were not removed and that they have recurred in the scar tissue. It seems to me imperative that the keloidal scar should be excised by a plastic surgeon, and to his discretion should be left what means to employ in order to obtain the best cosmetic result. I do not think it is always possible to tell the degree of malignancy in a melanotic growth clinically or histologically, and for that reason I suggest that whatever treatment is indicated should be done most thoroughly.

DR. GEORGE C. ANDREWS: One cannot compare melanoma in an infant with melanoma in an old man. It is well established that melanomas in children are less malignant than in adults. I am not worried about the melanomatous aspect of this lesion. However, I do feel that the treatment has made a "botch" of the appearance of the face, and I think it would be unwise to treat this keloid with radiation. In regard to Dr. Cannon's assertion that one must accept the microscopic analysis, the interpretation of early malignant changes in pigmented moles is difficult, and many times dermatologists will disagree on that point. I have known some of the best cancer pathologists to disagree widely as to whether a growth was melanocarcinoma or a melanoma irritated by trauma or infected. Therefore, I should not accept that report without knowing the person who made it or without knowing more about the section. I should not consign this child to a fatal ending because of that report, and certainly the statistics are much against the disease's having a fatal outcome in a child of this age. I do, however, agree with Dr. Cannon that excision and plastic repair are the best treatment for cosmetic reasons.

DR. HOWARD FOX: The question to settle without delay is whether the small pigmented lesions are recurrent melanocarcinomas. This could be easily done by excising one of these lesions for histologic study. I cannot see any justification for treating the keloid at present. Another question of practical interest is whether treatment by freezing is a safe one for hairy and pigmented moles which have been present since birth and which show no evidence of inflammation or increase in size. I still think this method of treatment is a proper one, in spite of an unusual experience I had in Bellevue Hospital. A girl of 15 with an ordinary hairy and pigmented mole of the face was treated several times with solid carbon dioxide, and, to the astonishment of all of the staff, this was later followed by melanocarcinoma, which was definitely proved.

DR. PAUL E. BECHET: I am also of the opinion that a biopsy of one of these "freckles" is advisable. Then the proper course to follow could be determined. In regard to pigmented moles, the question of future malignant changes always comes up. From a practical viewpoint these changes are rare. In the absence of trauma or ineffectual attempts at removal, I have observed such a change in very few instances.

DR. A. BENSON CANNON: The fact that the various members of this society hold such diverse opinions in regard to both the nature of the tumor removed and also the treatment would seem sufficient reason, in my estimation, why one should take no chances in this case. There should be a radical removal of the present keloid with the pigmented papules.

DR. EUGENE F. TRAUB: There are certain questions in this case that are difficult to answer, but some definite statements can be made. When this patient was first seen, the original lesion was about half again the size of the present scarred area or larger, measuring over 2 inches (5 cm.) in its greatest diameter. It can

be stated with certainty that had this patient been treated with solid carbon dioxide it would have caused a rapid dissemination of the malignant melanoma. There can be no doubt on this point, because here was a "junction" nevus that had already become a malignant melanoma before any treatment had been undertaken. Any local treatment would have sealed the child's fate, which is in doubt even after the radical removal that has been done. The excision was made by an excellent plastic surgeon, and when one considers the great size of the original nevus, the cosmetic result is not bad. Unfortunately the patient exhibited a tendency toward keloid formation both on the thigh, where the graft was obtained, and on the face. I thought from the onset that the lesion might be malignant; so it was widely and deeply excised. Therefore, perhaps the cosmetic result is not as good as might otherwise have been expected. It is probably fortunate that the graft took as well as it did under the circumstances. The section has been examined by a number of dermatologists, including Dr. Fraser, and every one who has seen it has looked on the growth as a malignant one. On this particular section there was no divergence of opinion. Sections of "junction" nevi submitted to a number of dermatologic pathologists frequently give rise to great differences of opinion as to the presence or absence of malignant change. The diagnosis therefore is difficult histologically and may not be settled on the microscopic picture alone. One of the features supposed to be indicative of malignant melanoma is illustrated well in this section, namely, the great amount of segregation or theque formation. The invasion deep into the fat layer is also noteworthy, and there are a number of other points which indicate that this lesion is an invasive one. The superficial pigmented spots, especially the one with the stellate shape, are not, in my opinion, the ordinary type of pigmented metastatic lesions in the skin. The latter are usually blue-black or slate colored, round and, as a rule, more deeply situated. The fact that this nevus was present from birth also makes for a better prognosis. It is the pigmented lesions that appear suddenly and later in life which offer a relatively bad prognosis when malignant melanoma intervenes. Therefore, taking all of these facts into consideration, I believe that it would be advisable to keep this patient under observation without doing anything, in fact, avoiding particularly a biopsy or treatment with radiation. My advice would be that if anything were done the entire lesion should again be excised completely, but because of the child's keloidal tendency the result might not be better cosmetically.

**Multiple Disseminated Angiomas.** Presented by DR. PAUL E. BECHET.

R. R., a man aged 30, presented from the New York Skin and Cancer Hospital, states that the lesions on the skin began when he was 16 years of age. For the first four years there was a rapid increase both in number and in size of the lesions. For the past ten years they have remained stationary. On inspection, most of the angiomas can be discerned on the buttocks, scrotum, shaft and glans of the penis, these areas being literally covered with them; on the inner aspects of the thighs and on the trunk they are sparsely scattered. They are deeply purplish red, pinhead to match head sized and so numerous on the buttocks that the left buttock is almost entirely covered. The lesions vary greatly in consistency; some are soft and others nodular. Some present a variable degree of elevation, while others are flat. The buccal mucosa is free.

A histologic examination showed in the upper part of the cutis directly under the epidermis several greatly dilated sinuses lined with a single layer of endothelium. The epidermis above these sinuses was thin and consisted for the most part of a few epidermal cells. The horny layer, which was slight, was made up of closely packed lamellas. The dilated sinuses were filled with blood and a few scattered polymorphonuclear leukocytes. The blood vessels of the upper part of the cutis were slightly dilated and surrounded by a sparse cellular infiltration composed of small round and occasional wandering connective tissue cells.

DISCUSSION

The members agreed unanimously with the diagnosis as presented.

**Basophilic Adenoma of the Pituitary (Cushing's Basophilism); Poikiloderma-Like Changes of the Skin.** Presented by DR. A. BENSON CANNON.

Mrs. R. S., a Russian Jewess aged 41, in the United States since 1922, has been a patient at the Vanderbilt Clinic at intervals since 1923, where she has been treated for atrophic telangiectatic changes in the skin attributed to a polyglandular dysfunction (of the thyroid and pituitary glands). This patient has been presented before a number of dermatologic organizations with varying diagnoses, the most frequent ones being angioma serpiginosum, poikiloderma vasculare atrophicans, radiodermatitis and pituitary adenoma. She had had roentgen ray treatment to the sides of her face seven years prior to admission for hypertrichosis. Dr. Irving Pardee published her case as one of pituitary basophilism (*Arch. Neurol. & Psychiat.* **31**:1007 [May] 1934), and Dr. Harvey Cushing in his discussion of this paper said that he considered her malady to be an "unmistakable example of pituitary basophilism."

The patient's symptoms have been headaches, general weakness, exophthalmos, pendulous breasts, large pendulous abdomen, obesity, hypertension, alopecia of the scalp, hypertrichosis of the face, extremities, back and chest and atrophy and telangiectasis of the skin of the cheeks, breast and abdomen.

The results of laboratory tests were essentially normal except that a roentgenogram of the skull showed decalcification of the skull and sella turcica.

Treatment has been mainly with thyroid, pituitary and iodine preparations. The condition has been slowly progressive, both in the cutaneous and in the mental manifestations. Perhaps the changes are not more than should be expected with age. The basal metabolic rate has advanced from —19 per cent in 1923 to practically normal (—6 per cent), probably as a result of treatment with glandular extracts.

DISCUSSION

DR. GEORGE C. ANDREWS: This patient's picture is in my textbook (Diseases of the Skin, W. B. Saunders Co., Philadelphia, page 165, second edition, published in 1939) under that diagnosis. She has changed considerably since then. She has lost weight. She also has much more body hair. The hirsutism on the chest is pronounced now, while before there were only two or three scattered long hairs on the breasts. I think the breasts are smaller than they were, probably as a result of the loss of weight.

DR. A. BENSON CANNON: Dr. Harvey Cushing, in discussing Dr. Pardee's presentation of this case together with 6 other cases, stated that the patient had an unmistakable basophilic adenoma of the pituitary. This patient and his second patient were the only 2 in a group of 7 that he thought had typical examples of the disease. He stressed the point that when one gland was diseased, it deranged the function of the entire glandular system, so that it was customary for the patient to have symptoms referable to each gland, as well as to the one primarily involved. He further called attention to the fact that many patients suffering with Cushing's syndrome showed no enlargement of the pituitary gland. At present the patient shows only a decalcification of the skull and sella turcica. I think that the changes in the palms and nails are probably due to an occupational dermatitis, or they may be of vascular origin.

**A Case for Diagnosis (Erythema Annulare Centrifugum of Darier?)** Presented by DR. FRED WISE.

F. H., a woman aged 30, registered at the New York Skin and Cancer Hospital on Nov. 8, 1941, with cutaneous lesions of one and one-half years' duration. She gives no history of any cutaneous disorders except for a "mild ringworm" on the leg at 17 years of age. In March 1940 she had a "streptococcic" sore throat followed by rheumatic fever. Two months before the eruption appeared the patient had been taking tablets of azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonate) and some laxative powders. Her general health has been good.

The initial lesions appeared in June 1940 in the left submental region, on the left upper eyelid and on the ankles, in the form of itchy ringed patches. A few

months later similar lesions developed on the right side of the chin and this year in the right popliteal area. They gradually spread until they reached their present dimensions, which are about twice their original size. There are roughly about a dozen lesions more or less symmetrically located in the aforementioned areas.

The most conspicuous and well defined lesions are situated on the left upper eyelid, on the anterior portion of the neck adjacent to the lower mandible (lateral submental regions) and in the right popliteal space. The one on the eyelid is oval and has an elevated pinkish border and a clear central area. The submental lesions are circular, with two or three rings fused edge to edge about 1½ inches (3.8 cm.) in diameter, with faintly elevated yellow borders and clear centers, resembling ordinary ringworm lesions. A similar circular patch, from which two specimens for biopsy were obtained, is present in the right popliteal space. On the anterior surface of the middle of the right ankle is a fairly uniform lesion 1 cm. in size with a pea-sized lighter central area. On the corresponding area on the left ankle is a similar-sized brownish red pigmented spot, which is apparently the result of a ringed lesion that has undergone regression. Diascopic pressure causes a fading of the borders, leaving a faintly perceptible uniform yellowish tint.

Routine laboratory tests and several examinations for ringworm, including cultures of the scales, gave negative results. The sedimentation rate was 24 mm. per hour (normal, 15 mm. per hour, Westergren method).

Histologic sections were examined by Dr. Charles F. Sims, who made a diagnosis of "long-standing dermatitis." The description is as follows: "The epidermis was fairly regularly and moderately acanthotic. The horny layer was slight and in part parakeratotic. The granular layer was present throughout the greater part of the section. Some exocytosis was present. In the papillary and subpapillary layers there was a moderate focal and diffuse cellular infiltration, composed of small round cells for the most part with an occasional wandering connective tissue cell. In the upper and middle parts of the cutis there was a moderate interstitial and parenchymatous edema of the collagen bundles. The vessels throughout the cutis were moderately dilated and congested, their walls somewhat edematous. A section was examined for mycelium; none was found.

NOTE.—The lesions subsequently faded out after three fractional (75 r) doses of unfiltered roentgen rays.

DISCUSSION

DR. GEORGE C. ANDREWS: I should advise another biopsy, especially of the lesion on the left upper eyelid, which is an annular lesion and which has some similarity to lichen planus. Also, lichenoid papules can be seen on the right side of the chin. Of course, the other linear lesions are not characteristic of lichen planus, but some of the microscopic features suggested that diagnosis to me. The lesions itch considerably, which is somewhat against the diagnosis of erythema annulare centrifugum. I believe, therefore, that lichen planus is a possibility.

DR. A. BENSON CANNON: At a glance the lesions look syphilitic. The unilateral appearance on one extremity, the circinate configuration, the elevation, the firmness and the brownish red color established them at once as being granulomatous. The scarring in the center of the lesion on the side of the knee and of the one on the ankle make me think of syphilis in spite of the negative serologic reactions. I suggest that another test of the blood be made and that the patient be given iodide and a few injections of a heavy metal. I should also repeat the biopsy.

DR J. GARDNER HOPKINS: I should like to add another diagnosis and that is circinate sarcoid. I had the same impression as Dr. Andrews, that the microscopic picture did not explain the clinical picture. I suggest taking a specimen for biopsy from another area.

**Parapsoriasis Maculata.** Presented by DR. FRANK C. COMBES.

E. P. H., a girl aged 15, had an eruption nine years ago on her forearms. Within a few months it became generalized but was devoid of any subjective

symptoms. About six months after its initial appearance it disappeared, but it returned two years later, and since then it has been stationary, although fading somewhat during the summer. At present it consists of many maculopapular lesions with almost imperceptible branny scales. Its color is variegated, and in some regions, such as the flexor aspects of the wrists, it suggests lichen planus.

DISCUSSION

The members agreed unanimously with the diagnosis as presented.

**Papulonecrotic Tuberculid. Tuberculous Adenitis. Dactylitis. Erythema Induratum.** Presented by DR. A. BENSON CANNON.

E. B., a Negress aged 27, married, a beautician, was admitted to Vanderbilt Clinic one week ago complaining of pain and swelling in the joints with limitation of motion of five years' duration. Her family history and past history were irrelevant. The present illness began in 1936, with pain and swelling in both ankles, enlarged left cervical lymph node and enlarged left axillary lymph node. The latter has continued to enlarge gradually since the onset. The swellings in the ankles and knees are recurrent, as is pain in the calves and thighs. Ten months ago pea-sized papules appeared on the elbows and on the shins and large tender swellings on the calves, with a few on the front of the thighs and on the abdomen. Many of these papules and nodules would become tender and ulcerate, discharging a thin blood-tinged purulent material. Healing was spontaneous. Six months ago several fingers became swollen and slightly painful. Both wrists, elbows, knees and hips have been painful. The patient has felt well except for the loss of 15 pounds (6.8 Kg.) in the last month.

Physical examination showed a well developed and nourished Negress with numerous pea-sized papules scattered over the aforementioned locations, with many pea-sized, deeply pitted scars. The papules varied from round to oval with central depressed necrosis. Some were ulcerated in the centers. On the calves and sides of the legs were hazelnut-sized, red, tender nodules, some of which were fluctuating and others had discharging sinuses. Several fingers showed uniform swelling with enlargement of the middle joint of the finger. The ulnar side of the left wrist was swollen to the size of an English walnut. There was a subcutaneous nodule, freely movable, nontender, in the left anterior axillary fold, the size of a hen's egg. The ankle joints were moderately swollen. There was no edema.

The Wassermann and Kline reactions were negative. The reaction to a test with old tuberculin was positive with 0.1 cc. of a 1:1,000,000 dilution. Roentgenograms of all the swollen joints and of the chest were essentially normal. Histologic examination of a papule taken from the thigh was suggestive of papulonecrotic tuberculid.

The patient has received two weekly injections of 0.1 and 0.15 Gm. of old arsphenamine. Improvement has been decided.

DISCUSSION

The members agreed unanimously with the diagnosis as presented.

**Leukoplakia of the Tongue.** Presented by DR. EUGENE F. TRAUB.

R. D., a man aged 42, was previously presented before this society in October 1929 (ARCH. DERMAT. & SYPH. **21**:509 [March] 1930).

At the previous presentation the oral condition was thought to be lichen planus, a diagnosis which was generally agreed with. Since presentation the patient has stopped smoking for a long period and without material improvement in the eruption. He has had five Wassermann tests, the reactions to all of which were negative. Recently he has had an occasional sore in the mouth and on the tongue, apparently aphthous stomatitis. Because of the discomfort of these transient lesions he again presented himself, and a biopsy was performed on one of the

lesions on the tongue. Dr. Barthel reported on the section as leukoplakia. The patient has been advised to discontinue smoking and to observe oral hygiene. He is presented for further therapeutic suggestions.

DISCUSSION

DR. J. FRANK FRASER: Notwithstanding the fact that the lesions present at the previous presentation were diagnosed as lichen planus, I feel convinced that the present condition is leukoplakia. It is known that leukoplakia is frequently reversible if the factors of irritation, such as smoking, are removed. The additional fact that in the great majority of cases leukoplakia never undergoes malignant transformation would be in favor of the view that this lesion should be left alone. Only 20 per cent, according to statistics, undergo malignant transformation. There is no evidence now from the gross appearance of any malignant change.

DR. GEORGE M. MACKEE: I leave patients with extensive leukoplakia alone except for advising oral hygiene and keeping them under observation. If there is the slightest sign of danger, such as verrucous development, persistent fissure, persistent ulcer or even persistent erosion, then treatment is indicated. At Memorial Hospital for the Treatment of Cancer and Allied Diseases a number of patients with leukoplakia have been treated with powdered brewers' yeast, 1 teaspoon three times daily for one month. Good results have been claimed with this treatment.

DR. FRED WISE: Patches of leukoplakia sometimes occur as a sequel to chronic eruptions of lichen planus of the tongue and buccal mucosa.

DR. GEORGE C. ANDREWS: I have had 2 cases in which epithelioma occurred in an area of lichen planus on the tongue. In reference to Dr. MacKee's remark about yeast, nicotinic acid of course has been used with success in some cases of leukoplakia. I have used it for conditions of the tongue like this with spectacular results at times and with no results at other times. It seems especially good for the inflammatory, ulcerative type of leukoplakia. I believe this man has a precancerous condition on the tongue, and whether to wait for cancer to develop or treat the lesions now is a problem. I should prefer, if it were my tongue, to have the lesion excised by a surgeon. It is surprising how good the plastic repair can be. I should make the excision deep enough so that the entire area of involved mucous membrane would be removed down to the muscle. That can be done satisfactorily by plastic surgery.

DR. A. BENSON CANNON: For twenty years or more I have removed leukoplakia from the mucous membranes of the mouth and tongue by electrodesiccation, and in a large series of cases I have never seen an ill result follow this method of therapy. My plan of procedure is to anesthetize the affected part with procaine hydrochloride and then desiccate the leukoplakic surface until it is white, spongy and slightly raised; after this the mucous membranes can be pulled off in great sheets, as one would remove the bark from a tree. There is little pain either during or after the operation. I have always endeavored to find the cause of leukoplakia; when one could attribute the condition to smoking and could have the patient discontinue the use of tobacco, I have usually noticed great improvement and sometimes a clearing up of the leukoplakia. When there is irritation from defective teeth, plates, et cetera, I seek to have them corrected. I think it is imperative to remove warty leukoplakias in order to prevent cancer. I have advocated thiamine therapy for leukoplakia for a number of years, and I have never noticed the disappearance of the leukoplakia after its use, although the doses might not have been large enough. The patient presented today has an unusually large tongue with atrophy in addition to the leukoplakia, symptoms one might expect in syphilis of the tongue.

DR. HOWARD FOX: One of the discussers spoke of lichen planus "turning into" leukoplakia. I do not understand how one could be sure of this unless a biopsy had been performed before this change took place. I refer only to lesions of the tongue in which the clinical differentiation is difficult or impossible. Lichen planus

of the buccal mucosa is usually characteristic, with its tiny white circles, dots and streaks. Opinions about treatment of leukoplakia vary from none at all except oral hygiene and cessation of smoking to radical removal. I agree entirely with Dr. MacKee that unless ulcers, nodules or fissures are present no radical treatment should be attempted. I have seen too many recurrences after such treatment. I wish Dr. Cannon would present some of the patients he has treated, especially after the lapse of a year or more.

DR. EUGENE F. TRAUB: Apparently at the time this patient was previously presented before this society there were lesions not only on the tongue but also on the buccal mucosa. Those on the buccal mucosa have practically disappeared. No one disagreed with the diagnosis of lichen planus at that time. The only question raised then by the various members was the method of treatment to be applied and the rebelliousness of the condition to therapy. The patient stopped smoking at that time, without any appreciable change in the lesions. He then returned to smoking. He presented himself about three months ago. He has again stopped smoking, and oral hygiene has been improved as much as possible with mild mouth washes and supervision of the teeth. He stated that every time he got a stomach upset, another type of lesion developed, a little erosion at the side of the tongue like an aphthous stomatitis. This was present tonight. It was for this that he sought treatment rather than for the leukoplakia. I will give him brewers' yeast or thiamine, as has been suggested. If local treatment were to be given, I should agree with Dr. Cannon's suggestion, because I have repeatedly used an electric loop and just shaved the surface, producing an excellent result.

DR. J. FRANK FRASER: Dr. Fox made the statement that he never saw an eruption like this clear up after smoking was discontinued. I have. I recall distinctly a case in which the condition was much more severe than that in this case, and the eruption cleared up after smoking was discontinued for one year. I believe other cases have been reported.

DR. GEORGE M. MACKEE: Are you sure the eruption is leukoplakia? I had a patient sent to me by a dentist with what seemed to me to be typical leukoplakia. The dentist told me that he had painted it with tincture of iodine and that it disappeared and then recurred. I did not believe him, but I tried this therapy and the white patches disappeared but soon recurred. The patches were then painted with gentian violet every day for a week or so. The eruption disappeared and never returned. Monilia albicans was found in cultures.

**Localized Lymphocytoma.** Presented by DR. FRED WISE.

S. F., a Negro aged 36, referred by Dr. Charles Kemm Good, registered at the New York Skin and Cancer Hospital on Dec. 27, 1941 complaining of swelling, eruption, itching, deformity and numbness of the right ear lobe and mastoid region. His general health has always been good. For the past year he has noticed that the right ear was being slowly "pushed forward."

Examination reveals a noticeable misplacement of the right auricle with diffuse swelling on its posterior surface, most pronounced on the lower half. From the middle of the free border of the ear lobe to the retroauricular fold is 3 cm., as compared with 1.5 cm. in the corresponding location on the left side. There is a fairly well demarcated area 2 by 3 cm. and 2 mm. thick on the upper border of the mastoid region, extending to about 1 cm. above the superior border of the pinna. The concha is twice the normal thickness.

There is a slightly raised, pinhead-sized to split pea–sized papular eruption distributed in an irregular, curved, broken-chain-like manner along the middle of the mastoid region and roughly parallel to and as long as the retroauricular fold. A few of the papules are fairly discrete, while most are fused. They are rounded, angular and irregular with flattened tops, somewhat indurated and apparently infiltrating all the layers of the epidermis but freely movable over the bony structures. The skin over the posterior surface of the auricle and mastoid region is taut, more darkly pigmented than the surrounding areas, with jet black

pigmentation accentuating the papular eruption. There is no evidence of atrophy. There is no cervical or inguinal adenopathy.

The hemogram was normal, and the results of routine laboratory tests were negative except the Wassermann reaction, which was positive. Roentgenograms of the chest and the involved areas of the skull did not reveal any pathologic changes.

A histologic section taken from the retroauricular region and examined by Dr. Charles F. Sims was diagnosed as lymphocytoma. The description was as follows: The epidermis was regularly acanthotic and was covered by a dense, slightly thickened horny layer. The cutis presented numerous masses of cellular infiltration which consisted of newly formed blood vessels, many lymphocytes and some large cells with vesicular nuclei and very little cytoplasm. This infiltration was present in a reticulum. In the deep part of the cutis there was a rather sharply defined area consisting of lymphocytes, all of which were more or less similar in their size and staining characteristics. Their nuclei were slightly larger than the usual small round cell, but the intranuclear network was more distinct than one finds in the common small round cell. Scattered throughout these masses there were also plasma cells and some wandering connective tissue cells. The blood vessels of the middle and deep portions of the cutis were moderately dilated, and their walls were edematous and presented an almost hyaline appearance. In some instances the lumens of these vessels were much narrowed. There was a moderate interstitial and parenchymatous edema throughout the cutis.

DISCUSSION

Dr. Howard Fox: Will the presenter say something about possible malignancy in this case? The disease has been present for five years and has not yet shown any such evidence. Localized lymphocytoma may be highly malignant, as in the case of a girl of 5 years whom I presented before this society (Arch. Dermat. & Syph. **6**:112 [July] 1922). The diagnosis was made by Dr. Douglas Symmers. The lesion flattened completely in five days after a single massive dose of roentgen rays, but other lesions appeared and the child died within six months.

Dr. George M. MacKee: I doubt that lymphocytoma would be so quickly fatal. Lymphosarcoma might disappear that quickly with roentgen ray treatment, and it might promptly recur.

Dr. Fred Wise: I do not believe that this variety of localized lymphocytoma is directly related to generalized leukemias. As a rule, the lesions are limited and circumscribed and the blood picture is unaffected. In this patient there is no evidence of adenopathy.

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## BROOKLYN DERMATOLOGICAL SOCIETY

L. M. Waterhouse, M.D., *President*

Seymour H. Silvers, M.D., *Secretary*

*Jan. 19, 1942*

**Erythema Nodosum.** Presented by Dr. C. T. Chiaramonte.

A. B., a white married woman aged 30, was admitted to the dermatologic service of Kings County Hospital on Jan. 11, 1942 with painful erythematous nodules on the extensor surfaces of the forearms and on the left knee. She gave a history of having had polyarthritis at 6 years of age and recurrent attacks until the age of 16, when she was hospitalized for five months for the condition. At that time she had cutaneous lesions.

Within the past month she has had three attacks of sore throat, the last one persisting for two weeks, until now; it is associated with malaise and drawing

aches in the thighs and lower part of the back, especially on the right side. One week before admission painful erythematous nodules developed on the extensor surface of the left forearm, and they soon appeared on the extensor surface of the right forearm and then on the left knee.

On admission the patient had raised, red tender nodular lesions on the extremities and pharyngitis. The temperature was 101.8 F. The cardiac examination revealed a questionable presystolic murmur. The other systems were normal. The patient was given salicylates internally.

At present the lesions have subsided, and the patient shows a raised, red, elevated plaque and a few scattered red nodules on the forearms and on the leg.

DISCUSSION

DR. ABRAHAM WALZER: I do not consider this condition a true example of erythema nodosum. At present the patient shows one big erythematous, slightly elevated plaque and scattered nodules on the arms and legs. I should call this disorder erythematous nodules in association with rheumatic fever.

DR. L. J. FRANK: It has been my impression that painful red nodules, tender to the touch, which do not suppurate and are associated with rheumatism are typical of erythema nodosum. Nodules may be associated with many other diseases, but I think this case is one of erythema nodosum.

DR. M. E. GOEBEL: One frequently encounters a case of rheumatic fever with articular and cutaneous involvement. The latter may take the form of erythema multiforme, in which one sees nodules with erythema or papules which last a certain length of time, depending on the infection. If erythema-nodosum-like lesions are present, with painful nodules occurring on the extensor surfaces of the extremities, the condition should be called erythema nodosum.

DR. ARTHUR W. GRACE: Some of the lesions seem more confluent than I am accustomed to seeing, but otherwise I consider the case a straightforward instance of erythema nodosum.

DR. JACOB SKEER: I have never seen erythema nodosum in such large plaques of exudative lesions. I should say the patient has a toxic eruption with erythema-nodosum-like nodules, for the nodular lesions which she presents do not concur with my conception of erythema nodosum.

DR. L. M. WATERHOUSE: I am inclined to agree with Dr. Skeer. These nodules are large, and I should expect them to be smaller in erythema nodosum.

DR. E. A. GAUVAIN: I agree with the diagnosis of erythema nodosum. It is true that some of the lesions are unusually large, but they are tender and infiltrated, as are those of erythema nodosum.

DR. D. M. DAVIDSON: The age of the patient, the location of the lesions and the tenderness and pain in the joints all are features which favor the diagnosis of erythema nodosum.

DR. L. FRUCHTBAUM: This case is a typical one of erythema nodosum. The patient gives a history of a similar attack at the age of 16. Tonight she shows the erythematous lesions and toxemia.

DR. LOUIS CHARGIN: I think the term erythema nodosum should be dropped. So many lesions are given this name which have no relation to what was originally described as erythema nodosum. One cannot on the basis of cutaneous lesions alone make a diagnosis of erythema nodosum. All one can say is that this patient presents numerous lesions with erythema. In this case, I should like to rule out a drug eruption, for bromides may produce a picture characteristic of erythema nodosum.

DR. ABRAHAM WALZER JR. (by invitation): When this patient was admitted to the hospital the lesions were slightly different from what they are tonight. The large plaque on the left knee consisted of about three or four small nodules which later became confluent. The patient was admitted with a diagnosis of rheumatic polyarthritis and possible heart disease.

**Lymphoblastoma (Lymphosarcoma? Leukemia?).** Presented by DR. C. T. CHIARAMONTE.

W. Mc., a white man aged 41, a waiter, entered Kings County Hospital on Nov. 4, 1941 complaining of a generalized eruption of four months' duration and enlarged glands of three weeks' duration. He had previously enjoyed good health and prior to the onset of the present illness took no medicine internally. There was nothing noteworthy in his past or familial history.

The redness and scaling first began on the extremities and gradually spread over the entire body. Later, the glands of the axillas, inguinal region and neck became enlarged. Prior to admission to the hospital the patient was studied clinically and by laboratory means, but no satisfactory diagnosis was made. Since his admission to the hospital these studies have been repeated and new ones made.

The laboratory findings were as follows: The values for urea, creatinine, uric acid and cholesterol were within normal limits. The Wassermann reaction was negative. The urine was normal. The blood agglutination reactions for typhoid, paratyphoid A and B, Brucella and Bacillus proteus were normal. The sedimentation rate was 8 mm. in two hours. Successive blood counts showed a gradual rise in the white cells from 6,200 per cubic millimeter on October 13 to 42,700 on December 13 and then a lowering to 23,200 on Jan. 6, 1942. The eosinophils varied from 1 to 6 per cent. The ratio of the other blood cells was within normal limits. Two bone marrow studies did not help to establish a final diagnosis. Roentgenograms of the bones and mediastinum did not show any abnormal masses. The histologic study of a lymph gland showed a loss of follicular structures with an infiltration of small round cells, plasma cells and many eosinophils; that of the skin showed hyperkeratosis, acanthosis, absence of the stratum granulosum and a papillary and subpapillary round cell infiltration, with some perivascular infiltration.

DISCUSSION

DR. JACOB SKEER: I believe the eruption is a lymphoblastoma. It is difficult to say at this time which type it is. Clinically the lesions on the scalp and face appear to me to be those of Hodgkin's disease. Further histologic studies should be made, and Hodgkin's disease should be ruled out.

DR. D. M. DAVIDSON: It was Symmers who was first to observe that there is a relation between erythroderma and enlargement of the lymph nodes with the histologic characteristics of a giant follicular lymphadenopathy. This may be the stage preceding Hodgkin's disease, leukemia or lymphosarcoma. The lesions at the onset of these diseases are variously diagnosed as contact dermatitis, chronic discoid dermatitis, mycosis fungoides, etc. I believe that the disorder in this case is Symmer's disease.

**A Case for Diagnosis (Pemphigus? Lupus Erythematosus?).** Presented by DR. C. T. CHIARAMONTE.

N. C., a white Italian woman aged 48, was admitted to the dermatologic service of Kings County Hospital on Nov. 24, 1941, with crusted blisters and areas of erythema and pigmentation over most of the body, especially on her back, arms, scalp and face.

One year ago, after using a hard brush on her scalp, she noticed a small weeping lesion on the vertex of the scalp. Shortly after this, following a permanent wave, several similar weeping lesions appeared on the scalp. She applied various salves and lotions, but the condition did not improve.

About six months ago she noticed a few blisters on the upper part of the back, which became crusted. Two months prior to admission, a private physician gave her intramuscular injections of a colorless liquid three times weekly. After the fourth injection she noticed new blisters on her back, shoulders and arms. After the seventh injection her eyelids became edematous and blisters appeared around the eyelids and spread over the face. The past history and family history are noncontributory.

On admission to the hospital she presented areas of erythema and ruptured bullae over the seborrheic areas of the back, arms and scalp. Areas of pigmentation from old healed lesions were seen on the lower part of the back. The forehead and upper part of the face were erythematous and edematous. Her scalp was scaly, and there was evidence of loss of hair. No oral lesions were present. The Nikolsky sign was positive.

The Wassermann reaction of the blood was negative. The urine was normal. The chemical examination of the blood showed no abnormalities. No arsenic was found in the urine. The blood count showed 4,100,000 red cells and 9,600 white cells, with 79 per cent polymorphonuclear leukocytes and 21 per cent lymphocytes. The hemoglobin content was 80 per cent. The histologic examination of one of the lesions was reported as showing pemphigus.

While in the hospital the patient received sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), sodium chloride and an extract of adrenal cortex (eschatin) internally and boric acid ointment, paste of zinc oxide N. F., sulfathiazole ointment and wool fat locally. Her face is still red, and occasionally new bullae appear. Her general condition is good.

DISCUSSION

DR. L. J. FRANK: I saw this patient a short time ago, when she showed slight scaling and oozing. Now the lesions look like those of pemphigus. Bullae in the mouth and on the scalp always make me suspect pemphigus.

DR. L. FRUCHTBAUM: I saw this patient at Long Island College Hospital seven months ago. She then had only crusting of the scalp with falling out of the hair at the vertex and no other lesions. I think she has pemphigus vulgaris.

DR. ABRAHAM WALZER: The Senear-Usher syndrome suggests lupus erythematosus, seborrhea and pemphigus. This patient has lesions on the face and back, and along the midline of the spine; the abdomen and the rest of the body are free from lesions. This is the distribution of seborrheic dermatitis. The lesions here are small, beginning as vesicles on an erythematous area. They become larger but are not typical of pemphigus. She has no lesions on the mucous membranes. The Nikolsky sign is present. I should accept a diagnosis of benign pemphigus.

DR. LOUIS CHARGIN: The disease in this case should be considered pemphigus. One may call it the Senear-Usher type. Histologic examination of the blisters shows pemphigus.

**Pemphigus Vulgaris.** Presented by DR. C. T. CHIARAMONTE.

G. L., a 44 year old Swedish man, was admitted to the Kings County Hospital on Nov. 19, 1942 with a generalized eruption of bullae of six months' duration. At the onset he noticed several small blisters on the vertex of the scalp, for which he sought medical attention. Ointments and roentgen ray therapy were used, with no beneficial results. Five weeks before admission blebs appeared on the inner surfaces of his arms and in both popliteal spaces. The bullous lesions spread gradually over the entire trunk and extremities. No oral lesions appeared. The past history and family history were irrelevant.

Examination shows the body to be covered with broken-down bullae. New bullae have developed, some having an erythematous areola and many arising from clear skin. The mouth, nose, genitals, palms and soles are free from lesions. The Wassermann reaction of the blood was negative. The urine was normal, as were the results of chemical examination of the blood.

An extract of adrenal cortex (eschatin) has been administered twice weekly for the past two weeks. In spite of treatment, new bullae appear daily, while older ones disappear.

DISCUSSION

DR. D. M. DAVIDSON: At present only the borders of the lesions suggest that they were bullae. In this case one must depend on the history to make a diagnosis of pemphigus vulgaris.

**Pemphigus Foliaceus.** Presented by DR. C. T. CHIARAMONTE.

C. G., a Jewess aged 55, was admitted to the Kings County Hospital on May 18, 1940 with an eruption of eleven months' duration. The lesions first appeared on the abdomen and gradually spread over the whole trunk. Five months before admission they had spread to the face and scalp, and two weeks prior to admission the legs and arms became involved. There have been no subjective complaints except for occasional chills and fever. There have been no oral lesions.

Examination reveals a generalized erythroderma. In certain regions of the abdomen flat blebs may be seen, which rupture so quickly that it is difficult to find them at any given time without careful search. The Nikolsky sign is positive.

Laboratory examination showed only a slight increase in eosinophils. Histologic examination was reported as showing exfoliative dermatitis.

A variety of internal and external medication was administered without appreciable improvement in the patient's condition. Intragluteal injections of an extract of adrenal cortex (eschatin) have recently been started.

DISCUSSION

DR. L. J. FRANK: This patient was in my service for about one year. She showed a great deal of scaling, redness and oozing, and a diagnosis of pemphigus foliaceus was made. At times she showed vesicles. Tonight bullae are seen; some are broken and crusted.

**Subacute Disseminated Lupus Erythematosus.** Presented by DR. C. T. CHIARAMONTE.

S. S., a white youth aged 18, came to the Kings County Hospital on Jan. 3, 1942 because of a "rash" on the body. Six months before admission, during the summer, he became sunburned while bathing at the seashore. A week after this initial exposure to the sun a small erythematous patch appeared on the bridge of the nose and on both cheeks, under the eyes. Shortly thereafter similar lesions appeared on the buttocks. During the ensuing summer the patient continued to expose himself to sunlight, clad only in bathing trunks. About the middle of August, following an unusually long exposure, the old lesions began to scale and new ones appeared on the face, forehead, neck and back. Since then the erythematous patches have spread to the trunk and extremities.

One month before admission the patient began to have palpitation, associated with fleeting precordial distress and mild exertional dyspnea. He also had recurrent attacks of pain in the left upper quadrant and chest, exaggerated by inspiration, and pain in the back of the neck, without limitation of motion or stiffness.

Examination shows the patient to be acutely ill, with a temperature of 100.2 F., a pulse rate of 72, a respiratory rate of 22 and blood pressure of 140 systolic and 80 diastolic. There is a diffuse, dusky erythema on the cheeks, ears and forehead. In these areas may be seen silver dollar–sized, dark red, oval to circular, discrete and confluent, sharply marginated, macular lesions. Many show atrophic centers with horny plugs. The arms, elbows and feet show some confluent lesions with fissuring and desquamation.

The hard and soft palate, as well as the buccal mucosa and gingival mucosa, show serpiginous marginated lesions with patchy gray central areas of necrosis. The heart is not enlarged, but there is a soft systolic blow at the apex transmitted to the axilla and a long harsh systolic murmur at the pulmonic region transmitted to the aortic and precordial regions. At the aortic region the murmur resembles that heard at the pulmonic region, but it is softer and is transmitted to the neck. There is regular sinus rhythm, and the sounds are loud and of good quality. The lungs are clear. The abdomen is normal.

The blood counts showed 6,500 to 7,500 white blood cells per cubic millimeter, with 67 to 70 per cent polymorphonuclear leukocytes and 30 per cent lymphocytes. There was a mild anemia: there were 3,800,000 red blood cells per cubic millimeter.

The Wassermann reaction was negative. The urinalysis showed a 1 plus reaction for albumin. The chemical examination of the blood showed no abnormalities, except for the urea content, which was elevated to 37 mg. per hundred cubic centimeters. Repeated cultures of the blood showed no organisms.

During his stay in the hospital the patient has had a continuous fever with a temperature range of 100 to 103.8 F. Large doses of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) were administered for seven days but did not influence the course of the fever. At present the patient is receiving 8 to 10 grains (0.5 to 0.65 Gm.) of quinine three times daily and is beginning to show some improvement. In addition, he is receiving large doses of vitamins A, B, C and D.

DISCUSSION

DR. LOUIS CHARGIN: The question arises as to whether this case is one of acute lupus erythematosus or disseminated lupus of the acute variety. Today it is difficult to make the diagnosis. The eruption on the face suggests the diagnosis of acute lupus erythematosus. The history is that the eruption began on the face, in butterfly arrangement, following sunburn, with considerable elevation of temperature, and the patient was rather ill. Therefore, in spite of the fact that the lesions on the body do not fit into the picture, I should say that the diagnosis is acute lupus erythematosus.

DR. JACOB SKEER: The lesions on the body do not fade out on pressure. Some lesions show brownish pigment. I have never seen this type of eruption with lupus erythematosus and do not know how to classify the lesions.

DR. ARTHUR W. GRACE: The cardiac lesion in lupus erythematosus is characteristic and different from the rheumatic carditis found in rheumatic fever.

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L. M. WATERHOUSE, M.D., *President*

SEYMOUR H. SILVERS, M.D., *Secretary*

*Feb. 16, 1942*

**Von Recklinghausen's Disease.** Presented by DR. D. M. DAVIDSON.

R. L., a white woman aged 25, is presented from the dermatologic clinic of the Cumberland Hospital with an eruption which she has had since birth. For the past few months she has been complaining of "fainting spells."

The patient presents a moderate number of pea-sized to nut-sized, soft and semifirm, fibromatous lesions on the trunk and extremities and one on the sole of the left foot. Some of the lesions are seemingly empty and disappear through a ring on pressure.

A large pendulous lesion occupies almost the entire left arm, and a smaller but similar lesion is in the left postauricular area. Brown pigmented areas are also scattered over the body. The patient's mother, who has similar lesions, claims that two other daughters are affected with the same disease.

**Adenoma Sebaceum (Pringle).** Presented by DR. D. M. DAVIDSON.

M. F., a white girl aged 8 years, is presented from the dermatologic clinic of the Cumberland Hospital. She has been suffering from epileptic seizures and has had a generalized eruption since birth, which is becoming progressively worse. There is no history of any other member of the family's having this disorder.

The patient shows an eruption on the face and body. On the face it consists of pinpoint-sized to pinhead-sized, colorless and reddish papules, which are more numerous on the nose and cheeks. There are also two erythematous and infiltrated plaques on the forehead. The trunk is covered with a moderate number of oval, pityriasis-rosaea-like lesions, which are similar in consistency to those on the forehead. Some depigmented areas and pinpoint-sized angiomas are also present on the trunk.

DISCUSSION

DR. ABRAHAM WALZER: The tendency to have neurofibromatosis is inherited as a dominant characteristic. I wish to call attention to the gingival fibromas grouped on the upper gum, which are supposed to be neurofibromas. I think there is a connection between von Recklinghausen's disease and adenoma sebaceum.

DR. L. FRUCHTBAUM: Nine years ago I presented a girl with extensive lesions of adenoma sebaceum. She had no lesions on the body at that time and no epilepsy. I treated the lesions by electrodesiccation, with good results. One year after I first saw her signs of a tumor of the brain developed. Roentgen therapy of high voltage was administered, and the patient improved. I saw her a few months ago, and she was well.

DR. J. SCHWEIG: The fundi should be examined for any evidence of a tumor, which is often found in tuberous sclerosis. The child presents another problem for study. She has angioneurotic edematous attacks, provoked by ingestion of sea food.

DR. JACOB SKEER: Some time ago I was fortunate enough to have a case of von Recklinghausen's disease with adenoma sebaceum, subungual fibromatosis and tuberous sclerosis (Skeer, J.: Adenoma Sebaceum [Pringle], von Recklinghausen's Disease, Subungual Fibromatosis Associated with Epilepsy or Tuberous Sclerosis: A Symptom Complex, *Urol. & Cutan. Rev.* **42**:110 [Feb.] 1938). The patient also had epilepsy (epiloia). A histologic section from the subungual lesion of the great toe showed hyperplasia of collagenous tissue and disintegration of elastic tissue. It was my opinion that all the lesions show similar histologic changes.

**Pemphigus Vulgaris.** Presented by DR. L. M. FRUCHTBAUM.

G. L., a Jewess aged 37, came to the Unity Hospital on Aug. 19, 1941 complaining of a lesion on the scalp of two weeks' duration. There was no history of any drug having been taken by mouth. During the next six months the patient returned at frequent intervals and at each visit to the clinic showed a further spread of the disease. Finally she showed extensive lesions of vesicles and bullae on the body and scalp and in the mouth.

Examination shows numerous flaccid bullae which arise from a noninflammatory base. Some contain serum and others serosanguinous fluid. The patient does not complain of itching. The lesions on the scalp are large and raised, but there is no loss of hair.

Various local remedies and sulfanilamide were tried, without success.

The Wassermann reaction of the blood was negative.

DISCUSSION

DR. M. M. ESTRIN: I believe that pemphigus need not end fatally. Unfortunately, the idea has been accepted that pemphigus leads to death, and if a patient does not die it is said that the disease was not pemphigus.

## MINNESOTA DERMATOLOGICAL SOCIETY

F. W. Lynch, M.D., *President*

H. A. Cumming, M.D., *Secretary*

*Minneapolis, Feb. 6, 1942*

**Mycosis Fungoides.** Presented by Dr. H. E. Michelson, Minneapolis.

A. C., a white farmer aged 68, was first seen in the University Clinics in March 1935, at which time he presented a generalized eruption consisting of cutaneous nodules and plaques varying in size from 1 to 3 cm. in diameter. The eruption was brown with shades of blue to red, and some of the lesions on the thighs were hemorrhagic. The face was free of eruption. There was a generalized, firm, painless adenopathy. Pruritus was present. There were no constitutional symptoms.

The lesions disappeared with roentgen therapy and did not recur for about a year. Subsequently the lesions reappeared on the lower extremities and again responded to roentgen therapy. During the last two months indurated weeping plaques developed on the neck and on the upper part of the thorax, with eczematous lesions on the legs and groin and generalized lymphadenopathy. He was much weaker than two months earlier.

**Mycosis Fungoides.** Presented by Dr. C. W. Laymon, Minneapolis.

Mrs. H., a white woman aged 69, complained of an eruption of twenty years' duration. A physician made a diagnosis of psoriasis ten years ago. Within the past year the lesions have become thickened and nodules have appeared.

Examination shows indurated brownish red nodules and plaques on the entire body, including the face. The histologic picture is consistent with the diagnosis of mycosis fungoides. Roentgen therapy has resulted in temporary involution of many of the lesions.

DISCUSSION OF TWO CASES OF MYCOSIS FUNGOIDES

Dr. Paul O'Leary, Rochester: Chaulmoogra oil injected intramuscularly and fever therapy are still used at the Mayo Clinic in the treatment of mycosis fungoides, with variable results. I wish I could say that the results were more encouraging. Two patients who had the early tumor phase of the disease when they were given chaulmoogra oil and hyperthermy treatment five or six years ago are still free from tumors, although they continue to have the eczematoid plaques of mycosis fungoides. In several other patients the continued use of roentgen therapy to the individual plaques has been necessary to keep the disease under control. Although discouragement has been more frequent than encouragement from the program, an occasional patient derives sufficient relief from the pruritus and the melting out of the early tumor lesions to warrant continued trial of the method.

**Psoriasis of the Palms and Soles.** Presented by Dr. S. E. Sweitzer, Minneapolis.

P. R., a white man aged 57, was treated for excessive sweating of the feet in 1919. He subsequently suffered from dryness and painful fissuring of the soles. Five or six years ago he noted a thickening of the affected areas. The fissures were so painful that the feet had to be kept taped constantly. Salves prescribed by physicians gave no relief. During the summer of 1941 thickened plaques with painful fissures and itching appeared on the palms. During the past few months the palms and soles have improved considerably with the use of boric acid ointment.

Examination now shows horny, thickened and fissured plaques of the hypothenar eminences of the palms, on the balls of the feet and on the heels. The microscopic examination confirmed the diagnosis.

DISCUSSION

DR. L. H. WINER, Minneapolis: At first glance this disease appeared as a mycotic dermatitis of the hands and feet, but on closer examination the correct diagnosis of psoriasis of the groin, palms and soles is evident.

**Keratosis Follicularis.** Presented by DR. H. E. MICHELSON, Minneapolis.

A. N., a white woman aged 25, first had an eruption on her neck when she was 7 years old, which gradually spread to the face and neck and to a lesser degree to the legs. Two sisters and the patient's mother were known to have a similar eruption.

Examination in early December 1941 showed grayish and brown papules on the face, neck, interscapular region, arms and legs. There were also some plaques covered by brownish crusts. From December 3, at which time the patient was first seen, to December 24 she was given 320,000 U. S. P. units of vitamin A daily. From Dec. 24 to Feb. 6, 1942 she was given 250,000 U. S. P. units of vitamin A daily. There has been much improvement in the condition of her skin.

DISCUSSION

DR. L. A. BRUNSTING, Rochester: I have encountered a number of instances in which benefit was obtained from the administration of vitamin A, one of the most remarkable being that of a patient who was presented at a meeting of the American Academy of Dermatology and Syphilology in December 1940 (ARCH. DERMAT. & SYPH. **44**:961-962 [Nov.] 1941). In general, the response of Darier's disease (keratosis follicularis) and Devergie's disease to vitamin A therapy is somewhat irregular.

DR. H. E. MICHELSON, Minneapolis: The eruption has faded considerably. When she was first seen, her face was masklike and cerise, and there was a large amount of scaling on the scalp. There were patches of scaling dermatitis on the elbows and knees, the edges of which faded out into follicular lesions. I feel certain of the diagnosis as presented.

**A Case for Diagnosis (Contact Dermatitis?).** Presented by DR. H. E. MICHELSON, Minneapolis.

K. T., a white woman aged 67, noticed an eruption on the right thigh underneath the garter a year ago. This eruption disappeared spontaneously but recurred a short time later and spread over both thighs. The lesions did not itch except when the patient bathed. She had taken various medications, including thyroid and laxatives.

Examination shows soft violaceous plaques on both thighs. There is no scaling, and there are no distinct papules. The lesions do not blanch completely on diascopic pressure.

DISCUSSION

DR. S. E. SWEITZER, Minneapolis: If the history is correct, this eruption might be contact dermatitis from her garters. Such a dermatitis usually itches, but the patient apparently has no symptoms. She first had an eruption which was largely vesicular with no itching. This may have been the result of chilling while she was standing out in the cold.

DR. L. H. WINER, Minneapolis: This disease was previously called contact dermatitis. Histologically, there were no atrophic changes in the epidermis. The cutis, however, showed changes around the network of blood vessels, where there was a perivascular infiltrate of round cells. This infiltrate extended down into the subcutis.

DR. C. W. LAYMON, Minneapolis: I first thought that this patient had lichen planus erythematosus, although sarcoid and pseudoxanthoma elasticum should be considered. The histologic picture could be fitted in with lichen planus. An elastic tissue stain should be made for further ruling out of pseudoxanthoma elasticum.

DR. H. E. MICHELSON, Minneapolis: Although this patient does not show an annular eruption, nevertheless a papular type was described, and erythema annulare centrifugum is a possible diagnosis.

**Boeck's Sarcoid Involving the Lymphatic System.** Presented by DR. H. E. MICHELSON, Minneapolis.

L. B., a white man aged 60, noticed enlarged glands in both groins about twelve years ago. He came to the University Hospitals in May 1940 because of swollen glands in the neck of three months' duration. Examination at that time revealed enlarged glands in the axillas and above the elbows, in addition to the cervical and inguinal adenopathy. He had a tremor of the head and his only other complaint was shortness of breath.

Histologic examination of an inguinal lymph gland in June 1940 showed the structure of the gland completely replaced by non-necrotic epithelioid and giant cell tubercles. Roentgenograms of the hands and chest on three occasions between June 1940 and January 1942 were normal.

In April 1941 a basal cell epithelioma on the left cheek was excised and nearby keratoses were cauterized.

In January 1942 histologic examination of an enlarged tonsil disclosed tubercles consisting of giant and epithelioid cells but no necrosis.

On examination at present, enlarged, firm and discrete nodes are felt on both sides of the neck, in the axillas, above the elbows and in both inguinal regions. There is a scar, the result of taking a specimen for biopsy, in the right groin. Otherwise examination reveals only keratoses on the face, a scar from the treated epithelioma on the left cheek and a healing furuncle on the anterior aspect of the left thigh.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: It is an interesting fact that a patient with sarcoidosis need not have cutaneous lesions. One thing I have learned in arriving at a diagnosis for patients without cutaneous lesions is that a biopsy of a specimen from the tonsils is not of much help. One must always perform an enucleation. In this patient the tonsil tissue is entirely replaced with typical sarcoid infiltration.

**A Case for Diagnosis (Telangiectasis?).** Presented by DR. S. E. SWEITZER, Minneapolis.

R. A., a white woman aged 43, first noticed a red patch on the left side of her neck fifteen years ago. She noticed a similar patch on the right side of her neck two years ago. She said that soap and water made the involved areas a "fiery red" and the remaining areas of the neck a diffuse, lighter red but did not affect the skin elsewhere. The patient also had neurodermatitis of the right ankle, which appeared ten years ago and was treated successfully with roentgen rays (600 r) here a year ago.

Examination shows tiny papules with surrounding telangiectatic areas. The lesions appear as irregular patches just below the ears.

DISCUSSION

DR. PAUL O'LEARY, Rochester: I thought this patient's disorder was a flushing or blushing reaction. There was a mild degree of involvement of both sides of the neck not related to pseudoatrophoderma colli, which affects primarily the back, chest and neck and has no erythema associated with it. Telangiectases and mild erythema in the V of the neck are frequently seen in persons who blush easily.

**A Case for Diagnosis (Schamberg's Disease? Acrodermatitis Chronica Atrophicans? Rosacea?).** Presented by DR. S. E. SWEITZER, Minneapolis.

A. F., a white man aged 70, had redness of the hands thirty to forty years ago. Most of his work was outdoors. Redness of the nose and cheeks appeared twenty to twenty-five years ago. Varicose veins of both legs had been present for eight to ten years. However, the patient experienced no pain in the legs. The first lesion on the right leg appeared one year ago. Other lesions appeared later in crops on both legs.

Examination of the legs shows discrete reddish brown spots which appear as irregular patches from the overlapping of adjacent lesions. These lesions are seen for the most part on the outer side of the right leg. There are a few brown spots on the left leg. Pinhead-sized red points also form irregular patches on the inner aspect of the right leg. The superficial veins of both legs are prominent and distended even when the patient is in a recumbent position. The skin of both hands is thin, wrinkled and pink, and there is a gradual fading into normal skin at the wrists. There are erythematous patches with telangiectasis and a minimal amount of pustulation on the nose and cheeks. The blood pressure was 220 systolic and 130 diastolic, but the patient gave no history suggestive of cardiac pain or decompensation.

DISCUSSION

DR. PAUL O'LEARY, Rochester: I agree with the diagnosis of rosacea. The patient also had varicosities, chronic dermatitis and residual pigmentation on the extremities. Some of his varicosities were as big as my thumb; so it would seem to me that the involvement of the legs is a stasis dermatitis with associated pigmentary changes and not a pigmentary dystrophy, as described by Schamberg.

DR. S. EPSTEIN, Marshfield, Wis.: I do not dare to give an opinion as to whether the lesion above the patient's ankle is enough reason to warrant the diagnosis of Schamberg's disease, but I do believe that there is a condition which corresponds to what is described as Schamberg's disease. Two days ago I saw a typical example of this chiefly covering the legs up to the knee but also involving the wrists and the region around the crena ani. There is definite atrophy on the back of the hand in this patient. I should not be able to make a diagnosis of acrodermatitis chronica atrophicans in this case, as I believe that a man 70 years of age who has spent most of his time working outside, exposed to sun and weather, is entitled to have senile atrophy of the skin. There were no lesions on the elbows or knees to indicate acrodermatitis chronica.

**Perlèche and Rosacea.** Presented by DR. S. E. SWEITZER, Minneapolis.

L. R., a white man aged 51, has noticed lesions about the lips for the last three months and on the tip of the nose for a year. Weakness was the only other complaint regarding his general health. His diet was apparently adequate. His past history revealed that he was a patient at Glen Lake Sanatorium, Oak Terrace, for a year, in 1932-1933, because of pulmonary tuberculosis involving the left lung.

On examination the lesions about the lips at the angles of the mouth show crusted fissures with surrounding erythema. There is a diffuse redness of the tip of the nose with pustulation, telangiectasis and also some fleshy hypertrophy. Some redness of the tongue is seen. The patient is now taking brewers' yeast.

DISCUSSION

DR. R. R. KIERLAND, Rochester: The cutaneous changes of this patient correspond to those attributed to riboflavin (vitamin $B_2$) deficiency. On the whole, however, I have been disappointed in the value of riboflavin or the whole vitamin B complex when used in the treatment of rosacea and rosacea keratitis.

DR. C. W. LAYMON, Minneapolis: In this case the perlèche will in all probability continue indefinitely unless dentures are properly adjust and fitted.

**Cysts of the Glands of Moll.** Presented by Dr. L. H. Winer, Minneapolis.

R. L., a white man aged 58, a jeweler, first noticed small masses on the margins of the upper and lower lids of the eyes about two years ago. The masses were symptomless and did not impair vision, and the patient thought that they could have been caused by a jeweler's eye loupe, which he wore over the right eye while working. On Dec. 9, 1941, with the patient under procaine hydrochloride anesthesia, the lesions of the left eyelids were clipped off; the sites of the lesions were cauterized, and they subsequently healed, with good cosmetic as well as good functional results.

Examination now shows pedunculated cystic masses, from 1 to 5 mm. in diameter and exuding clear fluid on perforation, on the outer margins of the right upper and lower eyelids and especially at the inner and outer angles of the eyelids. The left eyelids appear normal after therapy, as indicated in the history. Histologic sections were presented, which showed a cyst lined by epithelium usually two layers in thickness and located in the cutis.

DISCUSSION

Dr. L. H. Winer, Minneapolis: The cysts in this case are cysts of modified sweat glands adjacent to the ciliary hairs on the eyelashes and consist histologically of two layers of epithelium. Hidrocystomas are cysts of true sweat glands. The treatment is puncturing and cauterization.

**Dermatitis Factitia.** Presented by Dr. S. E. Sweitzer, Minneapolis.

E. K., a 48 year old housewife, had an eruption two months ago. There was itching, and the patient admitted that her eruption was to a large extent the result of scratching. She had passed the menopause six months earlier, felt nervous and weak and had a poor appetite. White spots on the skin had been present since childhood.

Examination shows flat papules of varying size covered with crusts of dried blood. The lesions are located on the upper part of the torso and are symmetric. On the upper part of the arms as well as on the upper part of the torso there are macular areas of depigmentation, also symmetrically distributed.

DISCUSSION

Dr. H. E. Michelson, Minneapolis: I disagree with the diagnosis of this case. Dermatitis factitia—or dermatitis autophytica, a term I prefer—is an eruption self induced with a desire to malign. This patient is distinctly of the neurotic type and openly admits producing the lesions. This type of patient often has a distinct psychogenic background, and the compulsions produced are because of unbearable physical elements or because of the subconscious conflicts. My diagnosis is neurotic excoriations.

Dr. F. W. Lynch, St. Paul: Dr. O'Leary, how often is hypnosis resorted to at the Mayo Clinic in cases such as this?

Dr. Paul O'Leary, Rochester: It is only occasionally that it is necessary to use hypnosis with drugs to elicit the background of a patient with factitial dermatitis. In most cases of this kind the history can be unraveled without resorting to the use of amytal; however, it has been a useful procedure when other methods fail.

# Directory of Dermatologic Societies *

## INTERNATIONAL

### Tenth International Congress of Dermatology and Syphilology

Oliver S. Ormsby, President, 25 E. Washington St., Chicago
Paul A. O'Leary, Secretary-General, 102-2d Ave. S. W., Rochester, Minn.
Place: New York. Time: Postponed indefinitely.

### Pan American Medical Association, Section of Dermatology and Syphilology

Austin W. Cheever, Secretary, 464 Beacon St., Boston.

## FOREIGN

### British Association of Dermatology and Syphilology (Canadian Branch)

B. Usher, President, 1538 Sherbrooke St. W., Montreal.
Frederick Kalz, Secretary-Treasurer, 1414 Drummond St., Montreal.

### Royal Society of Medicine, Section of Dermatology

H. W. Barber, President, 7 Devonshire Pl., London, W. 1, England.
Louis Forman, Secretary, 7 Devonshire Pl., London, W. 1, England.

## NATIONAL

### American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Clark W. Finnerud, Chairman, 55 E. Washington St., Chicago.
Nelson P. Anderson, Secretary, 2007 Wilshire Blvd., Los Angeles
Place: San Francisco.

### American Academy of Dermatology and Syphilology

Richard S. Weiss, President, 3720 Washington Blvd., St. Louis.
Earl D. Osborne, Secretary, 471 Delaware Ave., Buffalo, N. Y.

### American Board of Dermatology and Syphilology

Howard Fox, President, 140 E. 54th St., New York.
C. Guy Lane, Secretary-Treasurer, 416 Marlborough St., Boston.

### American Dermatological Association

William H. Guy, President, 500 Penn Ave., Pittsburgh.
Harry R. Foerster, Secretary, 208 E. Wisconsin Ave., Milwaukee.

### Society for Investigative Dermatology

Fred Wise, President, 200 W. 59th St., New York.
S. W. Becker, Secretary, University of Chicago, Department of Medicine, Chicago.
Place: Cleveland.

* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

## SECTIONAL

### Central States Dermatological Association

John E. Rauschkolb, Secretary-Treasurer, 1808 Republic Bldg., Cleveland.
Place: Cleveland. Time: Postponed indefinitely.

### Mississippi Valley Dermatological Society

Lawrence C. Goldberg, Secretary-Treasurer, 623 Doctors Bldg., Cincinnati.
Place: Chicago.

### New England Dermatological Society

John G. Downing, President, 520 Commonwealth Ave., Boston.
Francis M. Thurmon, Secretary, 520 Commonwealth Ave., Boston.

### Northern New Jersey Dermatological Society

John Kiley, President, 31 Lincoln Pk., Newark.
Henri Abel, Secretary, 339 Union Ave., Elizabeth.
Place: Academy of Medicine of Northern New Jersey, Newark. Time: Third Tuesday of March, April, October and December.

### Southeastern Dermatological Association

Howard King, Chairman, 328 Doctors Bldg., Nashville, Tenn.
J. Lamar Callaway, Secretary, Duke Hospital, Durham, N. C.

### Southern Medical Association, Section on Dermatology and Syphilology

Martin T. Van Studdiford, Chairman, 912 Pere Marquette Bldg., New Orleans.
J. Lamar Callaway, Secretary, Duke Hospital, Durham, N. C.

## STATE

### California Medical Association, Scientific Assembly, Dermatology and Syphilology Section

H. J. Templeton, Chairman, 3115 Webster St., Oakland.
Frances Torrey, Secretary, 123 Pemberton Pl., San Francisco.

### Connecticut State Medical Society, Section on Dermatology

Ralph E. McDonnell, Chairman, 158 Whitney Ave., New Haven.
Louis O'Brasky, Secretary, 1172 Chapel St., New Haven.

### Florida Society of Dermatology and Syphilology

Wiley M. Sams, Chairman, 25 S. E. 2d Ave., Miami.
Lauren M. Sompayrac, Secretary, 117 W. Duval St., Jacksonville.

### Louisiana Dermatological Society

M. T. Van Studdiford, President, 912 Pere Marquette Bldg., New Orleans.
R. A. Oriol, Secretary-Treasurer, 921 Canal St., New Orleans.

### Massachusetts Medical Society, Section on Dermatology and Syphilology

William Boardman, President, 388 Marlborough St., Boston.
J. H. Swartz, Secretary, 371 Commonwealth Ave., Boston.

### Medical Society of the State of New York, Section on Dermatology and Syphilology

George C. Andrews, Chairman, 115 E. 61st St., New York.
Richard L. Saunders, Secretary, 333 Linwood Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON DERMATOLOGY

Paul A. Deckard, Chairman, 814 N. 2d St., Harrisburg.
Bernhard A. Goldmann, Secretary, 500 Penn Ave., Pittsburgh.

MICHIGAN STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Frank Menaugh, Chairman, Ford Hospital, Detroit.
Eugene A. Hand, Secretary, 801 Second National Bank Bldg., Saginaw.

MINNESOTA DERMATOLOGICAL SOCIETY

H. E. Michelson, President, 825 Nicollet Ave., Minneapolis.
F. W. Lynch, Secretary-Treasurer, 317 Lowry Medical Arts Bldg., St. Paul.
Time: First Friday in October, December, February and April.

OKLAHOMA STATE DERMATOLOGICAL SOCIETY

John H. Lamb Jr., President, Medical Arts Bldg., Oklahoma City.
M. M. Wickham, Secretary, 716 W. Symmes St., Norman.

TEXAS DERMATOLOGICAL SOCIETY

Lewis Pipkin, President, 705 E. Houston St., San Antonio.
Duncan O. Poth, Secretary-Treasurer, 414 Navarro St., San Antonio.

## LOCAL

BALTIMORE-WASHINGTON DERMATOLOGICAL SOCIETY

Russell J. Fields, Chairman, 1726 I St. N. W., Washington, D. C.
Maurice Sullivan, Secretary-Treasurer, 11 E. Chase St., Baltimore.
Place: Alternate cities. Time: Third Thursday of each month.

BRONX DERMATOLOGICAL SOCIETY

Van Alstyne H. Cornell, President, 40 E. 61st St., New York.
Henry Silver, Secretary, 290 West End Ave., New York.
Time: Fourth Thursday of each month from October to May, inclusive.

BROOKLYN DERMATOLOGICAL SOCIETY

S. H. Silvers, President, 920 Bushwick Ave., Brooklyn.
M. Estrin, Secretary, 61 Eastern Parkway, Brooklyn.
Time: Third Monday of each month except June, July, August and September.

BUFFALO-ROCHESTER DERMATOLOGICAL SOCIETY

James W. Jordon, President, 471 Delaware Ave., Buffalo.
Frank A. Dolce, Secretary-Treasurer, 468 Delaware Ave., Buffalo.

CENTRAL NEW YORK DERMATOLOGICAL SOCIETY

Leon H. Griggs, President, 1804 State Tower Bldg., Syracuse.
Maxwell C. Snider, Secretary, 106 Oak St., Binghamton.

CHICAGO DERMATOLOGICAL SOCIETY

Udo J. Wile, President, 201 S. Main St., Ann Arbor, Mich.
Michael H. Ebert, Secretary-Treasurer, 25 E. Washington St., Chicago.

CINCINNATI SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

Harry L. Claasen, President, Provident Bank Bldg., Cincinnati.
Lawrence C. Goldberg, Secretary-Treasurer, 623 Doctors Bldg., Cincinnati.
Place: Cincinnati. Time: First Wednesday of each month, except July, August and September.

### Cleveland Dermatological Society

Charles G. La Rocco, President, 669 Rose Bldg., Cleveland.
John E. Rauschkolb, Secretary, 1808 Republic Bldg., Cleveland.

### Detroit Dermatological Society

George Van Rhee, President, 10 Peterboro Ave., Detroit.
John H. Besancon, Secretary-Treasurer, 1510 Eaton Tower, Detroit.

### Kansas City (Mo.) Dermatological Society

C. C. Dennie, President, 1103 Grand Ave., Kansas City.
Thomas B. Hall, Secretary, 902 Professional Bldg., Kansas City.

### Los Angeles Dermatological Society

Harry C. Lindsay, President, 595 E. Colorado St., Pasadena, Calif.
Saul S. Robinson, Secretary, 1930 Wilshire Blvd., Los Angeles.
Time: Second Tuesday of each month, October to May, inclusive.

### Manhattan Dermatologic Society

J. Frank Fraser, Chairman, 115 E. 61st St., New York.
Anthony C. Cipollaro, Secretary, 40 E. 61st St., New York.

### Montreal Dermatological Society

L. P. Ereaux, President, 1390 Sherbrooke St. W., Montreal, Canada.
Paul Poirier, Secretary, 456 Sherbrooke St. E., Montreal, Canada.

### New York Academy of Medicine, Section of Dermatology and Syphilis

Louis Tulipan, Chairman, 50 Park Ave., New York.
Timothy J. Riordan, Secretary, 136 E. 64th St., New York.

### New York Dermatological Society

Edward R. Maloney, President, 136 E. 64th St., New York.
J. Gardner Hopkins, Secretary-Treasurer, 630 W. 168th St., New York.

### Omaha Dermatological Society

Donald J. Wilson, President, 1113 Medical Arts Bldg., Omaha.
Leonard J. Owen, Secretary-Treasurer, 954 Stuart Bldg., Lincoln, Neb.

### Philadelphia Dermatological Society

A. Strauss, Chairman, 136 S. 16th St., Philadelphia.
Donald M. Pillsbury, Secretary, 133 S. 36th St., Philadelphia.
Time: Third Friday of each month from September to May, inclusive.

### Pittsburgh Dermatological Society

M. F. Pettler, President, 1319–8th Ave., Beaver Falls, Pa.
Joseph M. Shelton, Secretary, Washington Trust Bldg., Washington, Pa.
Time: Third Thursday of every month except July and August.

### St. Louis Dermatological Society

Norman Tobias, President, Missouri Theatre Bldg., St. Louis.
Joseph Grindon Jr., Secretary-Treasurer, 323 Lister Bldg., St. Louis.
Place: Barnard Free Skin and Cancer Hospital. Time: 2 p. m., second Wednesday of each month.

### San Francisco Dermatological Society

Arne E. Ingels, President, 490 Post St., San Francisco.
Ervin Epstein, Secretary-Treasurer, 1904 Franklin St., Oakland, Calif.
Time: Third Friday of February, April, September and November.

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